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Research Article

STUDY OF THE VIEWS ON PLACEBO AND ITS USE IN THE PEDIATRIC MEDICAL AND NURSING PRACTICE

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Abstract:

Background: The utilization of placebos intervention in clinical practice is generally controversial. This study aims to evaluate the use, knowledge, and attitudes about placebos among pediatric doctors and nurses.

Method: A survey-based cross-sectional study was used consisting of 19 questions, including prescribing frequency, type of placebo, indications, perceived effect, and ethical concerns associated with the use of placebos.

Result: Eighty-nine (29.5%) respondents prescribed placebos. The commonest placebo was saline infusion (16.6%). The commonest reason for prescribing placebos was to calm the patient and to stop him complaining (39.1%). Of the participants (83.8%) believed "placebos have therapeutic effects". 81.5% thought that its effect was psychological. Two-thirds felt that placebo should only be used selectively and 6% of thought that its use should always be permitted. 57.7% of doctors and 32% of nurses (P=0) think the patient should not know about the placebo.

Conclusion: Research about the use of placebo in clinical practice is still insignificant, particularly from the Middle East and in Saudi Arabia. In our study, nearly one-third of the respondents use placebos in clinical practice, which is lower than reported elsewhere. The vast majority felt that placebos are "sometimes effective" and a very small percentage believed that placebo prescription should be always permitted.

Keywords: Placebo, pediatrics, ethical concerns, physicians, nurses

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INTRODUCTION:

Placebo has been defined as an active or inert substance that is given to a patient instead of medication that may lead to some benefit due to a variety of psychophysiological factors. (1-3)

Research using placebo-controlled trials showed a possible beneficial placebo effect. However, the utilization of placebos intervention in clinical medicine is generally controversial. (4-7)

Its use is considered to be unethical for many reasons including the underlying deception in its use, (1, 7-9) its undermining of the patient's autonomy, (6, 10) (in children, they are subject to parental decision making on their behalf), (11, 12), its manipulation of the concepts of beneficence and non-maleficence. Furthermore, it may break trust in the doctor-patient-parents relationship. (5, 8, 12, 13)

On the other hand, it can be argued that it is justified in children as in adults with the purpose to benefiting the patient and when other effective treatment is lacking or when the placebo impact is known to be highly beneficial. (8) Some also argue that its use is acceptable if the physician informs the patient that he is providing a placebo. (7) One study showed that more than 86% of parents considered the use of placebos acceptable in some pediatric disease. (11)

Many believe that placebos work through psychobiological interventions through influencing the patient's anticipation and conception of their symptoms through personal experience or beliefs leading to the expectation of clinical benefit and by the physiological effects resulting from by pharmacologically active agents resulting in a positive therapeutic effect. (3, 8, 14, 15) For example, by evidence placebo intervention could lead to the production of endogenous opiates with major effects have been observed in pain, and indeed placebo works as analgesia. (16-19)

Many forms of placebo have been used in clinical practice, (14) One study showed that around two thirds of physicians used antibiotics against viral infections and more than half used vitamins, physiotherapy, and sedatives with no strong clinical indication. (5)

A systematic review of placebo use worldwide found that 17% to 80% of physicians used placebos during their career. (6, 8) In A cross-sectional studies, it was found that 17 to 99% of physicians (16, 20, 21) and 5 to 100% of nurses admitted using placebos. Other

studies confirmed that between 41% and 99% of doctors have used placebo. (5, 17, 22)

Not all doctors consider placebo use morally incorrect or useless. A number of studies have shown that, 50-90% of physicians and nurses believed that placebo treatments are generally effective. (5, 6, 16, 22)

In pediatrics, there are many clinical studies that addressed placebo effect in a variety of diseases including developmental/behavior diseases, allergic disease and neurological conditions. (19, 22, 23)

The indications for prescribing placebo are many and include satisfying the patients and their family, complying with expectations, avoiding arguments, (5) to reducing the diagnostic tests and calming a persistently demanding patient and taking advantage of the placebo effect in reducing pain, stress-related conditions, anxiety, and nausea. (6, 8, 9, 14, 16)

Few studies looked for placebo in Saudi Arabia, one study showed the frequency of the Saudi doctors prescribing a placebo is lower than in other countries. Around 80% of physicians believed that the placebo works through a psychological mechanism and they felt that placebos are at least "sometimes effective". (4)

We aim to evaluate the current use, knowledge, attitudes, and beliefs about placebos and the placebo effect among pediatrics practitioners in Saudi Arabia.

METHODOLOGY:

The study involved all pediatric practitioners (residents, specialists, consultants and nurses) in general and subspecialties of pediatrics in King Abdulaziz Medical City (KAMC), which is considered as a major tertiary children's hospital in Riyadh and the largest pediatric center in the Kingdom of Saudi Arabia.

A survey based cross-sectional study was used. The survey was sent to all the pediatric physicians and nurses electronically; explaining the purpose of the study and guaranteeing anonymity and an individualized online link to the research questionnaire. A reminder was sent two and four weeks later for those who have not responded. Additional email messages and word of mouth was also utilized to encourage maximum response rate.

The survey instrument consisted of 19 questions; 8 questions concerned demographic information (gender, age, nationality, religious affiliation, job

description, duration on the job and number of patients seen weekly) 11 basic multiple-choice questions related to use of placebos in routine clinical practice were asked, including prescribing frequency and type of placebo used, indications for its use, effect of placebos, perceived mode of action and ethics dilemma of use placebo in routine care.

While the majority of the questions were multiple choices, the questions on the types of placebos prescribed, indications of placebo use, mechanism of actions of treatment and ethical stances, all included an "other" response category for participants to customize their responses in an open-ended format and they can choose more than one answer.

Several of the survey questions were adapted from other previous studies and modified by the researcher. (4, 22, 24) The instrument was applied in English, two experts in the field assessed the modified version, and a pilot study was performed to assess its understandability.

The study was approved by the King Abdullah International Medical Research Center Institutional Review Board (IRB) (RC20/402/R). All participants consented to take part in the study and the responses were anonymous.

Statistical analysis:

The respondent (pediatric physicians and nurses) is the unit of analysis. In an exploratory analysis, Using Pearson Chi Square association, we compared the differences n between physician and nurses' characteristics such as age and sex, frequency of placebo use, beliefs regarding the therapeutic and ethical role of placebos in clinical practice, with a P value of less than 0.05 for statistical significance. Our results consist largely of frequency distributions of responses. The frequency totals add up to more than 100% for several questions for which practitioners were permitted to indicate more than one response. The analysis comprised of frequency distributions, cross tabulations, Chi square test, Odds ratio and student's t . test. All analyses were conducted with Statistical Package for Social Science (SPSS).

RESULT:

All pediatric physicians and nurses at KAMC were approached for the study and 302 responded (158 (50.62%) physicians and 144 (28.8%) nurses). A summary of the demographic and other characteristics of the participants are shown in Table 1.

Table 1: Demographic data.

Characteristics	No. (%) of 302 participants
Gender	
Male	75 (24.8)
Female	227 (75.2)
Age	
21-30	150 (49.7)
31-40	105 (34.8)
41-50	26 (8.6)
51-60	17 (5.6)
61-70	4 (1.3)
Nationality	
1= Saudi	166 (55.0)
2= Filipino	68 (22.5)
3= others	68 (22.5)
Religious	
1= Islam	211 (69.9)
2= Christianity	81 (26.8)
3= other	10 (3.3)
Duration on the job (years)	
1=<5	141 (46.7)
2= 5-10	96 (31.8)
3= >10	65 (21.5)
Job description	
1=nurse	144 (47.7)
2=resident	72 (23.8)

3=fellow	40 (13.2)
4= specialist	22 (7.3)
5= consultant	24 (7.9)
Pediatric specialty	
1= general pediatric	164 (54.3)
2= critical care	67 (22.2)
3= other pediatric subspecialties	71 (23.5)
Number of patient seen per week	
1= <10	52 (17.2)
2= 10-30	133 (44.0)
3= 31-50	57 (18.9)
4= 51-100	27 (8.9)
5= >100	33 (10.9)

Of the respondents, 89 (29.5%) stated that they used or prescribed placebo interventions, with 12 (4%) doing so almost weekly, 35 (11.6%) once a month, and 42 (13.9%) once a year.

The most common placebos were saline infusion (16.6%), vitamins in patients with no deficiency (14.6%), ibuprofen (7.6%), antibiotics for viral or other nonbacterial diagnoses (6.3%), sugar or artificial sweetener pills (6.3%). See Table 2.

Table 2: Types of treatments used as placebos.^a

Types of placebo	Yes (%)
1= Sugar or artificial sweetener pills	6.3%
2= Saline infusion	16.6%
3= Vitamins or dietary supplement	14.6%
4= Antibiotics	6.3%
5= Herbal supplements	1.3%
6= Alternative medicine ^{SEP}	1.0%
7= Ibuprofen or other pain medication	7.6%
8= Sub-therapeutic dose of medication	1.3%
9= An active substance that has no specific effect	2.0%
10= Practices or procedures that have no specific effect	1.3%
11= None	67.2%

^a As the respondents were allowed to choose more than 1 answer to a particular question, the percentages did not add up to 100.

Placebos were used in a variety of situations, the most common reasons were to calm the patient and to stop complaining (39.1%), as a diagnostic tool (i.e. to distinguish between psychogenic and organic causes of symptoms) (25.8%) and to control pain in 24.2%. Other reasons included “for non-specific complaints (15.9%), unjustified demand for medication (10.9%) and as an adjunctive therapy (9.9%), after all clinically indicated treatment possibilities were exhausted (6%), or to buy time (before starting actual therapy or between two doses of medicine) (4.6%).

Of the respondents, 37.4% did not find any indication for use placebo. We found doctors used placebos more as adjunctive therapy (15.2%) and as a diagnostic tool (12.2%) in comparison to nurses (4.2% and 15.35%, respectively) ($P < 0.002$). In contrast, nurses used placebo more for unjustified demand for medication (15.3%) compares to 7% of

doctors ($P=0.026$).

A majority of the participants (83.8%) believed “placebos have therapeutic effects” (9.3% “usually”, 74.5% “sometimes”) and 54.6% believed that “the placebo is equally effective in both genders as compared to 24.8% who thought that it is not effective in either genders. More doctors than nurses believed in the effectiveness of placebos (10.1% Vs. 8.3%, $P=0.0$) and more nurses (25.7%) thought it’s never effective compared to doctors (7.6%) ($P=0.0$).

Respondents were permitted to suggest more than one mechanism of action for placebos and 81.5% thought that the mechanism of placebo effects was psychological, while 4% believed that it was biochemical in nature; 9.6% thought that placebo works as a positive energy while (8.9%) thought that

the mechanism of placebo effects was unexplained; 16.3% had no idea about the mechanism and 5.6% thought it is not effective at all. No significant differences in the mechanism of action were observed between nurses and doctors except in “biochemical” and “positive energy” (doctors: 7%, 15.8% Vs. 0.7%, 2.8% of nurses respectively) ($P < 0.006$).

For ethical concerns, 66.6% felt that, placebo should be used only in select medical conditions; 37.4% opinioned that placebo should be used for research. Only 15.6% stated that placebo should never be used. More females than males believed the use of placebos is always unethical (19.8% Vs. 2.7%) ($P=0.0$) while more men agreed to use placebo for research purposes (52% Vs. 32.6%) ($P=0.003$).

Only 6% of respondents thought that placebo use was always permitted; 46.4% thought that placebo use was permissible if the results of clinical research supported its effectiveness and 26.5% considered placebo use to be justified if the experience of the medical staff supported its effectiveness. On the other hand, 8.3% thought it would be allowable after patients had been informed they would receive it.

Only (12.9%) of the respondents thought that placebo use in clinical practice should be always prohibited. 24.3% of nurses thought placebo should always prohibited Vs. 2.5% of doctors ($p=0$).

There are a number of ways to describe the nature of a placebo to the patient. In our study, 29.5 % described placebo as “actual medicine” and 12.3% made no comments about the placebo. Only 7.3% were truthful about the nature of the placebo with more doctors than nurses (11.4% Vs. 2.8%) ($P=0.0001$). At the same time, doctors are more likely to tell the patient that it is a real medication than nurses (37.2% Vs. 20.8%) ($P=0.0001$).

Just over half of participants think the patient should not know about placebo, (57.7% of doctors and 32% of nurses) ($P=0$). Around three quarter agreed to prescribe placebo for easing the patient’s suffering, pacify or silence the patient. Only 15.6% would refuse to give placebo in place of another medication that is expected to be more effective and 62.9% consider it to be unethical to discontinue a placebo if proved to be helpful. (Table3)

Table 3: Opinion of participants regarding certain ethical situations of using placebo.^a

Situation	Yes, always	Yes, sometimes	No at all
Do you think the patient should know about the placebo treatment?	46 (15.2)	101 (33.4)	155 (51.3)
A placebo can be prescribed for easing the patient’s suffering	156 (51.7)	96 (31.8)	50 (16.6)
A placebo can be prescribed to merely pacify the patient	147 (48.7)	94 (31.1)	61 (20.2)
A placebo can be prescribed to merely silence the patient	62 (20.5)	176 (58.3)	64 (21.2)
A placebo can be prescribed when failing to address the patient’s distress	82 (27.2)	174 (57.6)	46 (15.2)
A placebo use can be continued if proven ineffective	32 (10.6)	230 (76.2)	40 (13.2)
A placebo can be given in place of another medication that is expected to be more effective	37 (12.3)	218 (72.2)	47 (15.6)
When asked by the patient, a physician should be truthful about the placebo treatment you are offering	184 (60.9)	50 (16.6)	68 (22.5)
If a placebo helps, its discontinuation would be unethical.	77 (25.5)	113 (37.4)	112 (37.1)

^a Data are given as number (percentage) of participants (n = 302).

DISCUSSION:

In our study, only 29.5% prescribed or used placebo, which is similar to a study in Saudi Arabia (27.8 %). (4) In Europe, the prevalence of placebo use is over 80%. (5, 22, 25, 26) With less prevalence reported from USA, around half of internists and rheumatologists reported often recommending placebo treatments.(27) Just less than half (45%) among academic physicians in the Chicago, (16) and 56% of a random sample of US family physicians prescribe placebos. (20) In Poland, the frequency of the use placebo was much higher than in our study. (22)

In Poland the most popular placebo is a vitamin (66%) similar to German (62%) and Denmark (50%), (5, 22, 26) Vitamin use as a placebo was the second most common in our study, prescribing vitamins is not necessarily harmless. (28) In other hand, we found pure placebos (inert interventions, e.g. sugar pills or saline) were the most common type of placebo prescribed here in Saudi Arabia. (14)

Prescribing antibiotics for viral or other nonbacterial diagnoses was observed in 6.3% in our study but is the most frequent in USA (30-40%) with higher prevalence seen among general practitioners on Denmark (70%), (5, 16, 20) and 20% in Germany. This practice increases the level of resistance and has many other serious side effects. (29-32)

In our study, many respondents identified as one of the most common indications for placebo to “calm the patient and to stop complaining. Similar results were found in other studies. (5, 16, 27)

We found that more doctors used placebo as adjunctive therapy (15.2%) and as a diagnostic tool (12.2%) than nurses (4.2%, 15.35, respectively) ($P < 0.002$) This may be because the doctors are the ones responsible for the medical diagnosis and also because many clinicians still believe that the placebo effect can differentiate true from fabricated symptoms. (33)

For effectiveness of placebo; 83.8% of participants believed “placebos have therapeutic effects” (9.3% “usually,” 74.5% “sometimes,”), Same percentage was found in previous studies. (4, 20, 24) Respondents were permitted to propose more than one mechanism of action for placebos, (81.5%) thought that the mechanism of placebo effects was psychological, this thought is shared by many others in similar studies. (4, 14, 16, 24) This supports the concept that the power of mental thoughts over the physical health of our patients. (15) This may explain

the effect of complementary treatment such as meditation. (34, 35)

The views of the health practitioners on the ethics of placebo use were variable. There is significant difference between nurses and physicians regarding prohibition of placebo use, in our study 24.3% of nurses thought placebo should always be prohibited Vs. 2.5% of doctors ($P=0$); 30% of nurses. 6.6% of doctors believed that placebo prescription should always be prohibited. (4) This generally permissive behavior for physicians was found in many studies including in Saudi Arabia, (4, 14) as in many other studies. (16, 20, 22)

The reason for the belief that the use of placebo is unethical lies in that it misleads the patient and violates his autonomy and his right to know the nature of his treatment. (20) In our study, the biggest reason put forward that would make placebo use permissible was if the results of clinical research supported its effectiveness (46.4%), compared to 32-49% in other studies. (20, 22)

Doctors are more likely than nurses to declare the true nature of placebo to their patients. (11.4% Vs. 2.8%) ($P=0.0001$). This is contrary to another study from Saudi Arabia, which found more nurses than doctors to be truthful (42%) versus (2%). (4) This compared to only 2% of American Family Physicians,(20, 24) Among Swiss and American physicians, 64-68 % of those prescribing a placebo told the patient that it was a drug or a therapy. (25, 27) A higher percentage (80.76%) among Saudi health physicians described placebo as “medicine” to their patients. (14) The reluctance of many health practitioners to tell the truth of the placebo may be explained by fear of losing confidence by the patient or misunderstanding it as a kind of medical negligence. (13, 36) One of the solutions may be to take the consent from the patient at the beginning about all treatment possibilities, including placebo treatment. Certainly, more studies are needed on this issue. (37)

The study was a single center study. Additional multi-center is needed to be representative of pediatrics doctors and nurses in Saudi Arabia, even though it was conducted in the largest pediatric center in the Kingdom of Saudi Arabia.

The survey also relied on health practitioner’s retrospective self-reports and the data accordingly depended on their recall, social desirability, possible under-reporting of placebo use by some participants In addition to the meaning and concept of placebo

may be too broad for the participants to conceive. However, the similarity of most of our findings with previous studies suggests the possibility of its generalizability.

CONCLUSION:

Research about the use of placebo in clinical practice is still insignificant, particularly from the Middle East and in Saudi Arabia. In our study, nearly one third of the respondents use placebos in clinical practice, which is lower than reported elsewhere.

The commonest reason reported for the use of placebo treatments is to calm the patient and avoid conflict.

Two thirds of participants reported that they found placebo use to be only ethically acceptable in selected medical conditions. Most believe the mechanism of placebo effects is psychological. The vast majority felt that placebos are “sometimes effective” and very small percentage believed that placebo prescription should be always permitted. The reason for the belief that the use of placebo is unethical is that it misleads the patients and violates their autonomy and may lead to an adverse effect on the health provider and patient relationship as it may be perceived as deception by the patient. Only 7.3% of the respondents told the patients that it is actually placebos.

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REFERENCES:

1. Lichtenberg P, Heresco-Levy U, Nitzan U. The ethics of the placebo in clinical practice. *J Med Ethics*. 2004;30(6):551-4.
2. Louhiala P. What do we really know about the deliberate use of placebos in clinical practice? *J Med Ethics*. 2012;38(7):403-5.
3. Benedetti F. Placebo analgesia. *Neurol Sci*. 2006;27(2):006-0580.
4. Ahmed M, Kadhim D, Al-Seraya D, Nicholls M, Al Khader Al Sayyari A. Placebo Prescribing Habits And Views In A University Hospital. 2020.
5. Hróbjartsson A, Norup M. The use of placebo interventions in medical practice--a national questionnaire survey of Danish clinicians. *Eval Health Prof*. 2003;26(2):153-65.
6. Fässler M, Meissner K, Schneider A, Linde K. Frequency and circumstances of placebo use in clinical practice--a systematic review of empirical studies. *BMC Med*. 2010;8(15):1741-7015.
7. Cherniack EP. Would the elderly be better off if they were given more placebos? *Geriatr Gerontol Int*. 2010;10(2):131-7.
8. Hammami MM, Hammami S, Aboushaar R, Aljomah AS. Lay People's Ethical Attitudes To Placebo Treatment: A Q-Methodology Study. *Patient Prefer Adherence*. 2019;13:1599-617.
9. Petkovic G, Charlesworth JE, Kelley J, Miller F, Roberts N, Howick J. Effects of placebos without deception compared with no treatment: protocol for a systematic review and meta-analysis. *BMJ Open*. 2015;5(11):2015-009428.
10. Colloca L, Howick J. Placebos Without Deception: Outcomes, Mechanisms, and Ethics. *Int Rev Neurobiol*. 2018;138:219-40.
11. Faria V, Kossowsky J, Petkov MP, Kaptchuk TJ, Kirsch I, Lebel A, et al. Parental Attitudes About Placebo Use in Children. *J Pediatr*. 2017;181:272-8.
12. Gomez-diaz R, Rodarte N, Robles S, Aguilar-Salinas C. The Ethical Use of Placebo in Pediatric Research. *Journal of Clinical Research & Bioethics*. 2011;02.
13. Annoni M. The Ethics of Placebo Effects in Clinical Practice and Research. *Int Rev Neurobiol*. 2018;139:463-84.
14. Hassan T, Fauzi M, Hasan D. Perceptions of placebo therapy among health practitioners in Jazan region of Saudi Arabia. *Int J Health Sci*. 2011;5(1):45-9.
15. Colloca L, Benedetti F. Placebos and painkillers: is mind as real as matter? *Nat Rev Neurosci*. 2005;6(7):545-52.
16. Sherman R, Hickner J. Academic physicians use placebos in clinical practice and believe in the mind-body connection. *J Gen Intern Med*. 2008;23(1):7-10.
17. Bishop FL, Aizlewood L, Adams AE. When and why placebo-prescribing is acceptable and unacceptable: a focus group study of patients' views. *PLoS One*. 2014;9(7).
18. Ortiz R, Chandros Hull S, Colloca L. Patient attitudes about the clinical use of placebo: qualitative perspectives from a telephone survey. *BMJ Open*. 2016;6(4):2015-011012.
19. Pollo A, Benedetti F. The placebo response: neurobiological and clinical issues of neurological relevance. *Prog Brain Res*. 2009;175:283-94.
20. Kermen R, Hickner J, Brody H, Hasham I. Family physicians believe the placebo effect is therapeutic but often use real drugs as placebos. *Fam Med*. 2010;42(9):636-42.

21. Raz A, Campbell N, Guindi D, Holcroft C, Déry C, Cukier O. Placebos in clinical practice: comparing attitudes, beliefs, and patterns of use between academic psychiatrists and nonpsychiatrists. *Can J Psychiatry*. 2011;56(4):198-208.
22. Bąbel P. Use of placebo interventions in primary care in Poland. *Med Princ Pract*. 2013;22(5):484-8.
23. Simmons K, Ortiz R, Kossowsky J, Krummenacher P, Grillon C, Pine D, et al. Pain and placebo in pediatrics: a comprehensive review of laboratory and clinical findings. *Pain*. 2014;155(11):2229-35.
24. Nitzan U, Lichtenberg P. Questionnaire survey on use of placebo. *Bmj*. 2004;329(7472):944-6.
25. Fässler M, Gnädinger M, Rosemann T, Biller-Andorno N. Use of placebo interventions among Swiss primary care providers. *BMC Health Serv Res*. 2009;9(144):1472-6963.
26. Meissner K, Höfner L, Fässler M, Linde K. Widespread use of pure and impure placebo interventions by GPs in Germany. *Family practice*. 2011;29:79-85.
27. Tilburt JC, Emanuel EJ, Kaptchuk TJ, Curlin FA, Miller FG. Prescribing "placebo treatments": results of national survey of US internists and rheumatologists. *Bmj*. 2008;23(337).
28. Bjelakovic G, Nikolova D, Gluud LL, Simonetti RG, Gluud C. Mortality in randomized trials of antioxidant supplements for primary and secondary prevention: systematic review and meta-analysis. *Jama*. 2007;297(8):842-57.
29. Aslam B, Wang W, Arshad MI, Khurshid M, Muzammil S, Rasool MH, et al. Antibiotic resistance: a rundown of a global crisis. *Infect Drug Resist*. 2018;11:1645-58.
30. Ventola CL. The antibiotic resistance crisis: part 1: causes and threats. *P T*. 2015;40(4):277-83.
31. Stanley RJ, Tedesco FJ. Antibiotic-associated pseudomembranous colitis. *CRC Crit Rev Clin Radiol Nucl Med*. 1976;8(2):255-77.
32. Farooq PD, Urrunaga NH, Tang DM, von Rosenvinge EC. Pseudomembranous colitis. *Dis Mon*. 2015;61(5):181-206.
33. Goodwin JS, Goodwin JM, Vogel AV. Knowledge and use of placebos by house officers and nurses. *Ann Intern Med*. 1979;91(1):106-10.
34. Mommaerts JL, Devroey D. The placebo effect: how the subconscious fits in. *Perspect Biol Med*. 2012;55(1):43-58.
35. Thompson WG. Placebos: a review of the placebo response. *Am J Gastroenterol*. 2000;95(7):1637-43.
36. Trogen B, Caplan A, Klass P. The Ethics of Open-Label Placebos in Pediatrics. *Pediatrics*. 2017;140(2):2016-4328.
37. Miller FG, Colloca L. The legitimacy of placebo treatments in clinical practice: evidence and ethics. *Am J Bioeth*. 2009;9(12):39-47.