

General

Exploratory study of nocebo effect in senior medical students

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Keywords: nocebo effect, medical students, clinical context, adverse symptoms

<https://doi.org/10.52965/001c.117645>

Health Psychology Research

Vol. 12, 2024

Background

Nocebo Effect is known to induce adverse symptoms after negative expectations which can be manifested on a physical and psychological level. As 6th year medical students often face a wide range of clinical challenges and may be prone to negative expectations or beliefs affecting their pre-clinical and clinical success, we want to investigate how they are affected by the Nocebo Effect.

Objective

To investigate whether a nocebo effect can be induced when exposing final-year students to the clinical context of their training.

Methods

We used verbal suggestions as a nocebo mechanism and by using three tools, the Illness Attitude Scales, the Symptom Checklist-90, and the State-Trait Anxiety Inventory, we examined the difference in scores on measures of psychometric parameters in 33 participants who were on their 6th year medical and attended three clinics for the first time during their education. The administrations were given before and after attending each clinic, and negative verbal suggestions were given prior to the first administration. We also measured whether the overall number of clinics, had an effect on psychometric parameters.

Results

The results revealed a significant increase in second administration overall in the three clinics in specific psychometric parameters but no statistically significant difference was observed after attending consecutive clinics.

Conclusion

Students reported the occurrence of adverse symptoms in the investigated psychometric parameters, which should be noted in order to avoid potential educational clinical failure.

INTRODUCTION

The term “Nocebo Effect” refers to an intervention/procedure or the provision of an inert substance which aims either intentionally (e.g. disclosure of side effects) or unintentionally (e.g. exposure in a clinical setting) to produce adverse side effects¹ or often present as adverse effects to active treatments.² The main role in the Nocebo Effect is held by our belief system and it can arise through psychometric parameters that are imprinted on the person with various manifestations such as pain complaints, hypochondriasis, hyperalgesia and in general through the manifestation of various mental and physical negative symptoms.³

Also, from a neurobiological point of view, it has been showed that Nocebo Effect is due to a specific neurochemistry and is associated with a specific neural network.⁴

Even the mere disclosure by physicians or researchers of the possibility of experiencing increased physical or mental pain can create negative expectations and cause adverse mental and physical health outcomes as a consequence of Nocebo Effect.⁵

A key mechanism of Nocebo Effect is verbal suggestions that promote the formation of negative expectations or the absence of positive expectations.⁶ These findings have recently been replicated suggesting that verbal indications were those that created discomfort and headache.⁷ Verbal

suggestions, it has been shown in research, can also paradoxically modify the action of drugs.⁸ Research has also shown that conditioning learning can induce hyperalgesia and allodynia as a result of Nocebo Effect, using pharmacological as well as mental stimuli.^{9,10} Nocebo Effect may also be a result of social observation and interaction in which participants interact with and/or observe another person experiencing a negative symptom (e.g., pain).¹¹ Additionally, some studies have examined participants' negative expectations regarding the Nocebo Effect and pointed out the importance of emotions in its occurrence. More specifically, participants exposed to negative expectations report greater levels of anxiety,¹² worry,¹³ excitement and a lower sense of domination,⁴ as well as a general worsening of mood.¹⁴ The case is that negative emotions cause increased sensitivity to physical symptoms¹⁵ which makes it more likely that these symptoms will be highlighted and, in turn, linked to a specific treatment.

Nocebo Effect does not necessarily occur only through the administration of a substance or an intervention. Contextual factors such as the clinical context and therapist-patient interaction may form negative psychosocial perceptions that affect the magnitude of Nocebo Effect.¹⁶ In particular, the manifestation of Nocebo Effect has been investigated in clinical settings, where patients observe other patients interacting with health care personnel as well as their reactions to pain and treatment. According to this aspect, the clinical settings, which surrounds the administration of both active and nocebo interventions, is actively perceived by the patients, subjectively interpreted, and can induce the Nocebo Effect via conscious (e.g., memories, expectations) and non-conscious (e.g., escalation, emotions) cognitive or emotional processes.¹⁷

The clinical setting isn't a void dimension, but represents a powerful therapeutic space enriched by cognitive, emotional, affective, social and relational factors. Furthermore, it is possible for the clinical setting to interact with the patient's clinical condition.¹⁷ The factors of the clinical setting carry a hidden meaning, which is actively detected and analyzed by the patient and it is necessary for the perception of care and the interpretation of the therapeutic intervention¹⁸. When these factors are analyzed from the patient's perspective, they are interpreted into a complex barrage of psychoneuroimmunoendocrine events, capable of creating a Nocebo Effect and evoking expectations, memories, and emotions that, by extension, can influence the person's health-related outcome.

We do know from research that attending the School of Medicine bears down physically and mentally on a percentage of students. Various studies^{19,20} have investigated that the pre-clinical years of training in medical school, are related to the manifestation of mental disorders and psychological problems such as anxiety, depression, guilt, sadness and anger and in the occurrence of distressing symptoms related to the beliefs of students about their education,²¹ the attitude towards disease²² and students' burnout during medical education have been researched by recent study.²³ It is worth pointing out that students' emotional balance is essential for learning, decision-making and car-

ing skills²⁴ as high levels of anxiety and stress during their education can have negative effects on the learning procedure, affecting the preclinical and clinical success of the student.²⁵

Medical students often face a wide range of clinical challenges and may be prone to negative expectations or beliefs probably affecting their pre-clinical and clinical success. While the impact of the nocebo effect has been investigated for patients in clinical settings, we would like to investigate how it impacts senior students, as they come into contact for the first time with patients, the illness and the clinical context in general. Based on these premises, we conducted an exploratory study investigating Nocebo Effect on a sample of 6th year medical students who attended three clinics during their education.

MATERIALS AND METHODS

ETHICAL CONSIDERATION

The study was approved by the Medical Ethics Committee at the Eginition Hospital, Athens, Greece (Ω46Φ46Ψ8N2-33B. Protocol Number: 237_19). The study was conducted in accordance with the Declaration of Helsinki. All participants provided written informed consent. To ensure anonymity, protection of data and identification of students in attending clinics and in results matching, students were asked to write their first letter of the first and last name, date/month/time of birth, and the parents' names initials at the top of each psychometric tool form.

PARTICIPANTS

The sample came from the 6th year students of the Faculty of Medicine of the National and Kapodistrian University of Athens in two years' time who attended three educational clinics for the first time during their education: the 1st Pathology, the 1st Psychiatry and the 2nd Surgery clinic. As we could not include all 6th year medical students in the survey, we took as a basis the number of students attending the 1st Pathology clinic and then, based on their registration number, we follow up the students who attended the 1st psychiatry and the 2nd surgery clinic to create the necessary sample for our study. The students who constitute the sample of the study came from the program organized annually by the Secretariat of the Faculty of Medicine and during the last year they participate in both educational and clinical activities.

STUDY DESIGN

The study is a two-year prospective study on the investigation and arisen changes in the psychometric parameters of the Nocebo Effect among 6th year students of the Medical School of Athens. The format is a mixed model with comparisons between administrations (within subjects) and between subjects (between subjects) with a parametric procedure (2X3 Repeated Measures ANOVA) which is also the aim of the study. Individual comparisons (post-hoc) will be made with LSD (Least Significant Differences). The psycho-

metric tools of the study will be the dependent variables that will determine the effect of the Nocebo Effect and will be used to check whether the medical students manifest it to a greater extent in the second administration after attending the respective clinics. The null hypothesis is that students in both administrations and with the clinical burden will present similar scores on the questionnaires. The alternative hypothesis is that the students will present a higher score in the questionnaires State-Trait Anxiety, SCL-90 and Illness Attitude Scale after the end of attending each clinic, i.e. at the end of each educational period, the number of clinics 1, 2 or 3, will not act as an aggravating factor.

PROCEDURE

The study subjects were asked to fill in three psychometric tools related to their health attitudes, health symptom investigation and anxiety. The administration was carried out in two phases. The first administration was conducted on the first day of each clinic follow-up, at the lecture hall of the course. The students during the first administration - before completing the psychometric tools - they were asked for their consent to participate in the study signing an informed consent form. The study was presented by the researchers as a survey studying changes in students' attitudes towards their health after the stimulus of attending educational clinics and possible side effects. Then they were given verbal suggestions by the researchers that the forthcoming attendance of the educational clinic, the observation of the patients and the contact with the illness within this clinical setting, will probably cause them changes in their attitude and beliefs about their own health, and probably side effects as has been found by other similar studies.

The students were given the following verbal suggestion: "Previous studies has shown that healthy people who have been in a clinical setting and come into contact with patients and disease, had a negative change in their beliefs and attitudes about their health and side effects in psychosomatic level. Therefore, we expect that in the second administration and after attending the clinics, you will experience some changes which will be reflected in the psychometric tool measures". After the suggestion, the questionnaires and a file with demographic information were given to all students in the lecture hall who completed them in about 15 minutes. At the end of the 1st administration the researchers announced to the students that they will fill in the same questionnaires at the end of the clinic. The 2nd administration was conducted the last day of attendance of each clinic, again at the lecture hall of the class, without any suggestion. The time period of each clinic was four weeks, which includes educational and clinical activities. These activities include taking a medical history, writing notes for each patient and providing assistance to the medical team and faculty.

MATERIALS

In each administration, the students were first given three psychometric tools, the Illness Attitude Scales,²⁶ the Symptom Checklist-90 (SCL-90)²⁷ and the State-Trait Anxiety Inventory - STAI.²⁸ These psychometric instruments were chosen as they cover a wide range of psychometric parameters related to the nocebo effect and its side effects, as has been documented by previous studies.²⁹

The Illness Attitude Scales is a psychometric tool for the general assessment of fears and negative beliefs and attitudes related to hypochondriasis and abnormal illness behavior and includes nine scales. The Illness Attitude Scales was in English, so the second author translated it into the Modern Greek in consultation with a researcher specializing in mental health and then back-translated it in consultation with native English speakers to confirm the validity of the translation. The SCL-90 is an inventory of 90 self-report symptoms that characterize various psychiatric conditions. The SCL-90 is usually used to cover the last 7 days, but in the current study, it was used to cover the last 4 weeks of attending the respective training clinic. The State-Trait Anxiety Inventory (STAI) is one of the most well-known and widely used to measure anxiety and was used to measure situational anxiety (state) caused by stressful situations and to measure structural anxiety (trait) as a characteristic of the situation.

STATISTICAL ANALYSIS

Since the design adopted a 3X2 (3 clinics with 2 repeated measures) paradigm, the analysis most suited was a 3X2 ANOVA with one repeated measure. The suitability of the dependent variables for parametric analysis was verified with Levene's test for homogeneity of dependent variables. All dependent variables were clear for parametric analysis. To evaluate the results, Wilks' Lambda was calculated to confirm overall statistical significance before post hoc comparisons were made. Following Wilks' Lambda, post hoc comparisons were carried out using the Least Significant Differences procedure (LSD). This procedure was chosen for being 'liberal' enough as to avoid type two statistical errors. Analyses were two tailed and the 0.05 alpha level was used to signify statistical significance. All analyses were performed using the Statistica 13.5 software for Windows by Tibco Software (<https://www.statsoft.de/en/home/>)

RESULTS

According to the medical school schedule the whole student body does not attend the same clinics in an organized and linear way but are divided into many mixed groups, attending different clinics of the same specialty (e.g. 1st surgery clinic, 2nd surgery clinic, 2nd Pathological clinic etc). Therefore, having calculated the number of students attending the 1st Pathology Clinic as the basis for our study (1st year n=43, 2nd year n=54, total n=97), we looked at which students, based on the registration number, would then attend a psychiatry and a surgery clinic to create the

Table 1. Multivariate Tests of Significance (Wilks' Lambda)

	Test	Value	F	Effect df	Error df	p	Partial eta-squared	Observed power
Clinics	L	0,792828	0,5158	42	176	0,993	0,454	0,999
Measurements (1st-2nd)		0,546383	3,4790	21	88	0,000	0,454	
Clinics x Measurements (1st-2nd)		0,680293	0,8901	42	176	0,664	0,454	

necessary sample for our study. This resulted in some of the initial sample ($n=64$) not being included in the study because they attended different clinics based on their schedule or attended only two or one of the clinics surveyed. The final sample included 33 subjects (1st year $n=17$, 2nd year $n=16$). There were no exclusion criteria and 24 of them were women and 9 men who had completed attending the three clinics. The mean age of women was 24.08 with a SD = 1.61, of men 24 with a SD = 0.60 and the group as a whole was 24.05 years with a SD = 1.35 and an age range of 7 years (minimum 23 and maximum 30). As for the age of the two sexes no statistically significant differences emerged ($F = 0.028$, $p = 0.869$).

A statistically significant Wilks' Lambda was obtained for the repetition (1st and 2nd administration) of the measurements and then individual comparisons were made to calculate the statistical significance with the LSD (Least Significant Differences) index and the effect sizes (effect sizes) with the Partial eta-squared index (Table 1). No statistically significant Wilks' Lambda index emerged for the clinics and for the interaction between clinics and measures. The results according to the LSD (Least Significant Differences) post hoc evaluation reveal a statistically significant increase in the score from the 1st to the 2nd administration in specific psychometric parameters related to changes in beliefs about pain and subjective perception of physical and psychological dysfunction.

Specifically, the measure at the 2nd administration for the psychometric parameter Concerns About Pain was significantly higher ($M (SD) = 5.38 (2.58)$); $F = 17.002$, $p < .001$, $\eta_p^2 = 0.136$ compared to the first administration ($M (SD) = 4.79 (2.51)$). Similar significantly higher scores were shown in the 2nd administration for the psychometric parameter Hypochondriacal Beliefs ($M (SD) = 2.45 (2.23)$); $F = 39.907$, $p < .001$, $\eta_p^2 = 0.270$, in Disease Phobia ($M (SD) = 2.68 (2.11)$); $F = 26.123$, $p < .001$, $\eta_p^2 = 0.195$ in comparison to the 1st administration for Hypochondriacal Beliefs ($M (SD) = 1.48 (1.54)$) and Disease Phobia ($M (SD) = 2.04 (1.94)$). All three psychometric parameters that were $p < .001$ belonged to the Illness Attitude Scale psychometric tool.

On the SCL-90 scale, there were also significant increases in the second administration in the Somatization parameter ($M (SD) = 6.05 (6.19)$); $F = 4.215$, $p = .042$, $\eta_p^2 = 0.038$ compared to the first administration ($M (SD) = 5.27 (6.29)$) and in the second administration of the Depression parameter ($M (SD) = 10.42 (6.47)$); $F = 6.266$, $p = .014$, $\eta_p^2 = 0.055$, compared to the first administration ($M (SD) = 9.65 (6.33)$). Also, on the Anxiety parameter, the second admin-

istration showed significantly higher scores ($M (SD) = 9.77 (8.76)$); $F = 4.851$, $p = .030$, $\eta_p^2 = 0.043$ compared to the first administration ($M (SD) = 8.80 (8.56)$) and finally in the Hostility parameter the scores in the second administration were significantly increased ($M (SD) = 4.30 (4.53)$); $F = 4.135$, $p = .044$, $\eta_p^2 = 0.037$ whereas in the first administration the scores were lower ($M (SD) = 3.68 (4.73)$). Finally, in the STAI tool, Trait Anxiety parameter showed a significant increase in the second administration with scores ($M (SD) = 48 (9.07)$); $F = 5.409$, $p = .022$, $\eta_p^2 = 0.048$ in contrast to the first administration ($M (SD) = 46.77 (9.98)$). Mixed results derived from the remaining parameters. In the parameters Effects of Symptoms ($p = 0.221$), Interpersonal Sensitivity ($p = 0.132$) and State Anxiety ($p = 0.069$) the measurements during the 2nd administration revealed a small increase but not statistically significant. In the remaining parameters, Worry about Illness ($p = 0.334$), Bodily Preoccupation ($p = 0.442$), Thanatophobia ($p = 0.517$), Health Habits ($p = 0.684$), Treatment Experiences ($p = 0.588$), Phobic Anxiety ($p = 0.592$), Paranoid Ideation ($p = 0.325$), Psychoticism ($p = 0.305$) there was no statistically significant difference (Table 2).

Finally, the analysis regarding the clinics revealed no significant differences between them, regardless of administrations and timeline, i.e. 1st and 2nd clinic, 2nd and 3rd clinic and 1st and 3rd clinic (Figure 1).

DISCUSSION

The current study investigated whether negative verbal suggestions would induce self-reported changes in physical and psychological levels as a result of the nocebo effect in senior medical students after attending three clinics and whether the number of clinics would be an aggravating factor that would be reflected in changes in psychometric parameters. Overall, the study findings illustrate that verbal suggestions probably shaped negative expectations in senior students about side effects at the psychosomatic level after contact with the clinical setting. Verbal suggestions have been researched to have a distinct dynamic and likely lead to the formation of negative expectations, as has been found in previous research.³⁰

In the parameters with significant increase, small effect sizes were also observed, but they were significant. However, no significant results were seen in the psychometric parameters after continuous follow-up of the clinics and between them.

Table 2. Means and LSD results for 1st and 2nd Administration

	MEAN (CI: -95%- +95%)	SD	MEAN (CI: -95%- +95%)	SD	F	p (Least Significant Differences)	Partial eta- squared
Worry about illness	4,68 (4,20-5,17)	2,58	4,81 (4,30-5,32)	2,72	0,940	0,334	0,009
Concerns about pain	4,79 (4,32-5,26)	2,51	5,38 (4,89-5,86)	2,58	17,002	0,000	0,136
Health habits	6,61 (6,17-7,05)	2,33	6,56 (6,08-7,04)	2,56	0,167	0,684	0,002
Hypochondriacal beliefs	1,48 (1,19-1,77)	1,54	2,45 (2,03-2,87)	2,23	39,907	0,000	0,270
Thanatophobia	3,03 (2,61-3,45)	2,23	3,14 (2,70-3,57)	2,31	0,517	0,517	0,004
Disease Phobia	2,04 (1,67-2,40)	1,94	2,68 (2,29-3,08)	2,11	26,123	0,000	0,195
Bodily preoccupation	3,12 (2,75-3,49)	1,96	3,23 (2,82-3,65)	2,20	0,594	0,442	0,005
Treatment experience	3,36 (3,08-3,84)	2,04	3,52 (3,10-3,94)	2,23	0,588	0,588	0,003
Effects of symptoms	2,53 (2,08-2,99)	2,42	2,72 (2,22-3,22)	2,65	0,221	0,221	0,014
Somatization	5,27 (4,09-6,45)	6,29	6,05 (4,89-7,22)	6,19	4,215	0,042	0,038
Obsessive-Compulsive	9,05 (7,93-10,17)	5,96	9,39 (8,27-10,51)	5,95	0,963	0,329	0,009
Interpersonal sensitivity	7,36 (6,31-8,41)	5,58	7,81 (6,72-8,90)	5,79	2,308	0,132	0,021
Depression	9,65 (8,46-10,84)	6,33	10,42 (9,21-11,64)	6,47	6,2663	0,014	0,055
Anxiety	8,80 (7,19-10,41)	8,56	9,77 (8,13-11,42)	8,76	4,8512	0,030	0,043
Hostility	3,68 (2,80-4,57)	4,73	4,30 (3,45-5,15)	4,53	4,135	0,044	0,037
Phobic Anxiety	3,72 (3,03-4,41)	3,65	3,82 (3,14-4,50)	3,61	0,289	0,592	0,003
Paranoid Ideation	1,73 (1,36-2,10)	1,99	1,89 (1,48-2,31)	2,20	0,979	0,325	0,009
Psychoticism	3,86 (3,26-4,47)	3,23	4,07 (3,50-4,64)	3,04	1,064	0,305	0,010
State Anxiety	44,50 (42,62-46,39)	10,04	45,72 (44,06-47,38)	8,83	3,364	0,069	0,030
Trait Anxiety	46,77 (44,90-48,65)	9,98	48,00 (46,29-49,71)	9,07	5,409	0,022	0,048

The choice of clinics reflected a wider scale of medical training, with illnesses that are risky to people's health and can cause significant problems to people's psychosomatic health or even death. While attending the three clinics, the final year students found themselves for the first time, together with the team of physician-teachers, visiting patients who had been diagnosed with mental and physical illnesses, getting in touch with the disease and knowing details about the course of the disease.

The results of three scales of the Illness Attitude Scales - Concerns about Pain, Hypochondriacal Beliefs and Disease Phobia showed $p < .001$ while significant results were

obtained on the SCL-90 Somatization, Depression, Anxiety and Hostility scales and the STAI Trait Anxiety scale.

The Concerns about Pain psychometric parameter of the Illness Attitudes Scales captured in the study, refers to the recognition of physical pain and the creation of concern that it may be indicative of an underlying disease. Pain recognition and feeling related to Nocebo Effect is a key finding in many studies and with many expressions after verbal suggestions and social observation as shown by the meta-analyses of Petersen et al³¹ and Blasini et al.¹ The senior medical students are exposed for the first time to direct and live observation of patients' pain during their clinical training and it was investigated the fact that they reported

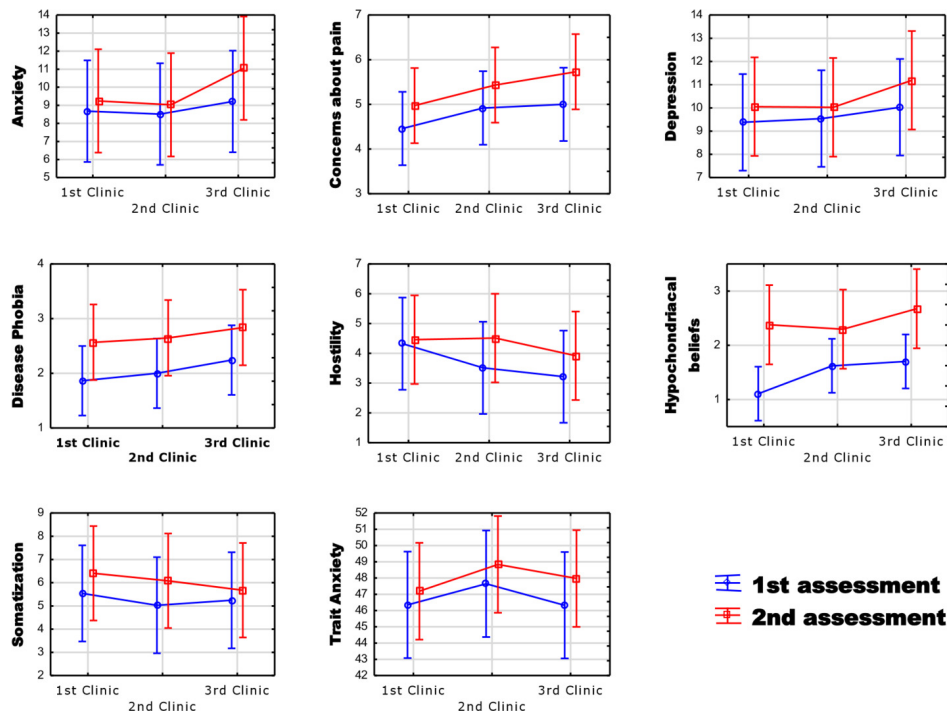


Figure 1. Interaction Clinics x Measurements: illustrating the first and second administrations and the interaction between clinics for the psychometric parameters.

thoughts and concerns related to the presence of pain and its connection with a serious illness, i.e. negative beliefs caused by the fear of pain and other medical procedures.³²

A related result is the psychometric parameter of Somatization of the SCL-90 scale, which refers to distress resulting from physical symptoms, such as discomforts on the cardiovascular, gastrointestinal, respiratory, and other organ systems and are reflections of a physical illness. The participants were exposed to a variety of diseases during their training to the three clinics and as a result, in combination with the verbal suggestions of the researchers, it was recorded the finding of somatization, as a possible Nocebo Effect, without however having specific reports on that, as there were no relevant questions at the psychometric tools. The high frequency of exposure to the disease in addition to verbal suggestions about possible symptoms and the observation of others creating negative expectations is also a strong predictor of Nocebo Effect, as reflected in a systematic review.²⁹ These results are related to other studies that used guiding verbal suggestions for possible negative symptoms and affected the psychometric parameter of somatosensory perception³³ and the capture of other symptoms such as nausea³⁴ palpitations and increased blood pressure³⁵ and abdominal pain and headache.³⁶

The additional psychometric parameters Hypochondriacal Beliefs and Disease Phobia maintain a common psychological background. The appearance of both parameters supports the consistency of the findings as they both refer to the maximization of physical symptoms such as headaches, gastro problems and other physical discomforts that may manifest as illness in individuals when in fact they were not ill. The subjective perception of physical discomfort when observing other people suffering has been found

to be correlated to Nocebo Effect, in a research level as has the maximization of symptoms following verbal suggestions of recognized associations.³⁷ As we do not know the specific symptoms that were perceived or maximized by the subjects of the research, we assume that there were, to a lesser extent, physical discomforts related to the diseases they faced in the training clinics.

The psychometric parameters Anxiety of the SCL-90 and Trait Anxiety of the STAI were also significant findings. Anxiety, which is one of the negative emotions, has been investigated to be associated with the manifestation of Nocebo Effect. It is presented in research as an intermediary factor that mediates between verbal suggestions and negative expectations and Nocebo Effect.³⁸ In addition, anxiety in students is reflected on the one hand with its emotional dimension through students' anxiety and phobia and on the other hand and as a physical symptom such as tremors and palpitations³⁹; symptoms that probably indicate the stress they experienced during in the clinical setting.

Trait Anxiety, is a stable pattern of reaction and behavior and is a personality characteristic. We make the hypothesis that trait anxiety pre-exists in some subjects and may experience attending the clinic as a stressful situation, perceiving it as dangerous or threatening for them, and it is related to the psychometric parameters of Somatization and Concerns about Pain as a Nocebo Effect. This finding is related to a similar one presented in a previous study⁴⁰ that anxiety preceding verbal suggestion can increase subsequent expectations of harmful consequences and possibly provides an explanation why people with anxiety are more susceptible to the Nocebo Effect.

The last two parameters with a statistical important score are Depression and Hostility and are related to emo-

tion and behavior. The Depression parameter, which reflects symptoms of dysphoric emotions and mood such as lack of motivation, interest, and signs of withdrawal, is a finding that- we suppose- it is associated with the mental distress experienced by students through the stimulus of disease and patients, uncertainty, and probably death; a topic they have studied in theory but they are facing it clinically for the first time. The effect of depression has also been shown in other research related to medical school students.²⁰ To the best of our knowledge as for the literature, studies relating depression to Nocebo Effect concern either the response of depressed patients to the Nocebo Effect with administration of fluoxetine or a placebo⁴¹ or adverse events after a placebo intervention in clinical trials for the treatment of depression.⁴²

Finally, an increased score was observed in the psychometric parameter of Hostility, which is an unrecognized emotion of emotional disorders.⁴³ Hostility is a finding that has not, at least to our knowledge, been found in other studies of Nocebo Effect although it has been shown in previous research to be a psychological parameter that manifests itself in medical students, with the appearance of physical symptoms.⁴⁴ However, we know that research is associated with increased anxiety as a starting point that can lead to feelings of hostility⁴⁵ and manifest as well discomfort and the manifestation of aggressive acts. We suppose that the students' exposure to serious and health-threatening illnesses may have been emotionally exhausting and contributed to the creation of aggressive feelings that were not recorded as behaviors. Having the knowledge that in general the increased scores in the scales of the SCL-90 reflect the corresponding clinical syndromes and don't identify them linearly, we cannot argue that the students presented a corresponding psychopathology but a corresponding dysphoric tendency related to Nocebo Effect.

In the interaction between the clinics, no statistically significant interaction and changes in the psychometric parameters were found. However, some parameters increased between 1st and 2nd clinic, 2nd and 3rd clinic, as well as between 1st and 3rd clinic. However, the results were within the statistical error and found $p > 0.05$. That is, there was an increase which may indicate a small burden on the students with the continuous monitoring of the clinics; however, this was not statistically confirmed. The effect was relatively short as the transition to the next clinics did not contribute to the persistence of the increased scores of the psychometric parameters. As the attendance of the three clinics was not consecutive but they also attended other clinics in between with reduced contact with the disease (e.g. forensic medicine, paediatrics, obstetrics) or there was a time gap based on the course of study of the Faculty, we assume that this intervention was an ameliorative factor on the results. However, at a later stage, the cumulative effect of all clinics of the senior year could be investigated.

LIMITATIONS

The limitations of the study are initially presented in the relatively, but consistent, small sample, focused on specific clinics and included students from only one medicine

school, so the findings cannot be universalized on a wider scale. Also, a screening was not done to see if some students who participated in the study had certain psychological characteristics that were related to the psychometric parameters we were examining. Moreover, the order of attending clinics wasn't the same for all students, resulting in different clinics being interjected before attending the clinics under research. Furthermore, the time periods of observation of the sample were quite long and it wasn't possible to know whether the students confronted some other biopsychosocial or stressful condition between the administrations.

CONCLUSION

According to our knowledge, this is the first research that investigates the psychometric parameters of Nocebo Effect in senior medical students during the attendance of specific educational clinics. For senior medical students, Nocebo Effect may be particularly critical because they are often exposed to a wide range of treatments and procedures and may be prone to negative expectations or beliefs about them. The findings of the research showed the increase in some psychometric parameters negatively associated with mental and physical health. As senior students directly enter the professional field after graduation, awareness of Nocebo Effect becomes more important as concerns arise as to whether these negative beliefs persist and may affect them in their clinical work and not knowing that Nocebo Effect can affect the therapeutic relationship and communication with patients with possible side effects on therapeutic adherence.

To minimize the Nocebo Effect, it is important that medical students are aware of the phenomenon and approach treatments and educational processes with an open mind. They should also be aware of their own biases and beliefs and try to maintain objectivity when evaluating treatments and procedures. Understanding the Nocebo Effect within educational clinical settings can help educators develop appropriate interventions aimed at increasing students' awareness and competence in the field of medicine. Future research on the topic of Nocebo Effect may include a control group from another university, which although included in the initial design of this study due to the unexpected appearance of SARS-CoV-2 couldn't be included in the continuation of the research as it would alter the reliability of the comparison of the samples. Also, in subsequent research, the personality parameter can be measured in order to distinguish those elements of medical students that are more related to the Nocebo Effect and then to create more specialized interventions.

ACKNOWLEDGMENTS

The authors would like to thank all participating students in this study and directors, professors and secretaries of

each clinic for their support with the administration of the psychometric tools.

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All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

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CONFLICTS OF INTEREST

All authors have declared no conflict of interest and that no financial support was received from any organization for the submitted work.

CONFERENCE PRESENTATION

The study was accepted and presented on the 31st Annual Conference of the Greek Psychiatry Association, 25-28 May 2023.

Submitted: April 20, 2024 EST, Accepted: April 26, 2024 EST

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