

Knowledge and Perception Toward Neuromodulation Devices Among Medical Students at Umm Al-Qura University

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Abstract

Introduction

Neurologic and psychiatric disorders affect many people worldwide and are crucial to medical care. It is crucial to note that primary care doctors initially evaluate patients who will eventually require neuromodulation (NM) therapy. There is a growing concern about the extent of medical students' knowledge regarding NM therapy. Insufficient education and limited exposure of future doctors to different treatment approaches can limit their ability to refer patients promptly and appropriately, thereby impeding access to necessary treatment.

Methods

The study employed a non-probability stratified snowball sampling technique to recruit participants. The population consisted of undergraduate medical students (excluding interns) at Umm Al-Qura University in Saudi Arabia. Data collection was conducted through an online questionnaire.

Results

The sample comprised 301 medical students, with an average age of 21.62 ± 1.54 years (ranging from 18 to 25). The majority were female (65.1%), and in the clinical years (57.8%), a considerable portion of respondents (57.5%) lacked awareness that NM devices are approved by the FDA for treatment. Both pre-clinical and clinical-year students exhibited insufficient knowledge (91.3% and 91.4%, respectively). Females showed a higher proportion (95.9%) of poor attitudes towards NM compared to males (83.8%). Notably, preclinical students showed a higher level of knowledge (11.0%) compared to clinical students (6.3%).

Conclusions

The study revealed a significant lack of knowledge among medical students regarding NM devices. This is concerning given the growing prevalence of NM devices in clinical practice. To ensure optimal patient care, it is crucial to provide comprehensive education on NM devices to medical students.

Categories: Neurology, Psychiatry, Neurosurgery

Keywords: psychiatric disorders, uqu, medical education, students' knowledge, neurologic disorders, neuromodulation

Introduction

Neurologic and psychiatric disorders affect millions of people worldwide, and in medical care, they are regularly encountered and typically linked with poor outcomes [1]. It is therefore important to note that inadequate education or exposure of future doctors to treatment modalities may adversely affect their ability to make timely and appropriate referrals to ultimately provide patients with the treatment they require.

Neuromodulation (NM) is a fast-growing field of neurotechnology that offers modulative effects on the central or peripheral nervous systems. NM involves the placement of electrodes into precise neural targets with the purpose of administering physical energy and modifying deviant brain activity. Consequently, suppressing a particular diseased area can restore a healthy neural system [2]. As a result of recent advancements in neurotechnology, neuroimaging, and neurocircuitry, the effectiveness of neurostimulation devices has continued to rise over time to treat an expanding variety of neurologic and psychiatric issues [3].

Vagal nerve stimulation (VNS) and the responsive neurostimulation system (RNS) are two NM devices that

have been approved by the Food and Drug Administration (FDA) for treating epilepsy [4-7]. Nowadays, NM is the standard of care for treating drug-resistant Parkinson's disease as a more effective and less-complication-associated alternative to ablative surgical procedures. Other diseases have received FDA approval, such as essential tremors, dystonia, and obsessive-compulsive disorder. Similarly, intermittent theta-burst stimulation (iTBS) for the treatment of resistant depression has also received FDA approval [8].

In addition, NM has become a gold standard therapy in motor circuit disorders due to advances made over the last two decades; several clinical trials have also studied its efficacy in other emerging nonmotor indications [9,10]. Despite the growing number of patients who undergo NM yearly, this therapeutic modality is still underutilized for a variety of different reasons [8].

Besides technical and clinical challenges, patients' expectations must be considered, in addition to the knowledge level among medical students and general practitioners. As most patients who will be referred to NM at some point during their disorder will be seen first by primary care physicians.

Medical students' knowledge about NM therapy has been a concern. In a study involved students at Hannover Medical School who were asked to fill out a questionnaire that included questions about DBS throughout their pre-clinical study period and in their last year of study. They showed partial awareness of DBS in the preclinical years, but as they continued their studies, their knowledge expanded in the following years [11].

On the contrary, a study at Virginia Tech Carilion School of Medicine, which involved 65 medical students, found no differences between the surveyed pre-clinical and clinical students regarding knowledge of DBS [12].

Currently, there are no specific guidelines for medical education in NM; exposure to these devices is likely important in improving medical students' knowledge and comfort level. In another study conducted to assess the knowledge level regarding electroconvulsive therapy (ECT), medical students who have been exposed to such a treatment modality were proven to be more knowledgeable [13]. Similarly, the use of video-based educational materials resulted in a measurable improvement in students' knowledge and attitudes regarding ECT [14]. These studies suggest that the direct exposure component of medical education may be important.

Little is known about the knowledge level of NM devices among medical students. To obtain a deep insight into this area and to identify in which aspects medical students' knowledge is lacking, this study aims to explore the current knowledge and attitude of Umm Al-Qura University (UQU) medical students toward NM devices as a treatment modality and to compare clinical and pre-clinical years.

Materials And Methods

Study design

While Umm Al-Qura University's medical curriculum includes some exposure to relevant topics, such as neuroscience and behavior in the third year (pre-clinical) with 7 weeks of basic science, and clinical neurology in the fourth year (clinical) with 2 weeks of theoretical as a part of other topics in medicine followed by two weeks for neurology clinical placements, it should be noted that neuromodulation devices are not comprehensively covered in all years. These topics may only be briefly mentioned rather than extensively taught in the curriculum. Psychiatry, which is covered in the fifth year (clinical) under the name of Mental Health, with a total of 14 theoretical lectures and only 1 week of clinical placement. A descriptive cross-sectional study was undertaken to evaluate the knowledge and perception pertaining to NM devices among medical students at the University of Umm Al-Qura in Saudi Arabia, spanning the period from February 2023 to April 2023. Employing a non-probability stratified snowball sampling methodology, participants were recruited. The data collection process employed an online questionnaire, which was subsequently integrated into Google Forms. This instrument was electronically administered to the respondents, primarily through the utilization of social media platforms, with a significant emphasis on WhatsApp as the primary medium of dissemination. In order to ensure a precise and targeted allocation of the questionnaire, the WhatsApp contact details of the students were collected with the assistance of data collectors from each academic batch, who collaborated with the authors in the data collection phase.

Study Population

The study's target population was all undergraduate medical students who gave their consent to participate in the survey at UQU in Makkah, Saudi Arabia. Interns were excluded.

Sampling methodology and data collection

The sample size was calculated using OpenEpi version 3.0. The university's academic affairs department estimated the number of all academic years' medical students at around 1400. The calculation of the sample size was based on a 95% confidence interval (CI) with 50% frequency and a design effect of 1. 300 medical

students were required at least. The sample was distributed equally among the academic years. As for the study tool, an organized, self-administered online questionnaire was used to collect data.

The questionnaire was adopted from another survey study with some modifications to cover NM devices in general [12]. The survey consisted of a 25-item questionnaire, including a demographic section, a knowledge inventory to assess attitudes toward NM, and a self-perceived education on NM. Additionally, there is an independent item, a self-assessment of knowledge. The questions on knowledge and self-perception of education were multiple choice (yes = 1, I don't know = 0, and no = -1). Whereas attitude responses were based on a five-point Likert scale, scores of 1, 0.5, 0, -0.5, and -1 were assigned for each of the answers. Finally, the sum of knowledge and attitude questions was graded as "good" and "positive," respectively, if the score was 60% or higher; participants who had a score of more than 5 are considered to have good knowledge, and more than 4 are considered to have a good attitude. Self-assessment of knowledge was measured by asking students to judge their understanding of NM on a 7-point scale (1 = vague understanding to 7 = thorough understanding).

Data Analysis

A nonparametric, univariate analysis was performed. A descriptive analysis was conducted based on frequencies and percentages for categorical variables. A Chi-square test was used to assess the associations between the variables. Significance was assumed at $p < 0.05$ for all tests. The data were analyzed using BlueSky Statistics version 10.2.1 (Chicago, IL: BlueSky Statistics LLC).

Results

A total of 301 study participants were included in this study according to the inclusion and exclusion criteria; none were excluded. Table 1 represents demographic information about the sample population. The sample consists of 301 medical students, with a mean age of 21.62 ± 1.54 (range 18-25 years). The majority of the sample is female (65.1%), and most participants (57.8%) are in the clinical years of the study (years 4, 5, and 6). Regarding the intended medical specialties of the participants in the 7 specialties listed, medicine was the most popular choice among the participants (16.0%), followed by general surgery (13.6%). Notably, more than 30% of the participants are undecided about their intended specialty. In addition, upon asking participants whether they have a family member who has been treated with NM devices, most of the respondents (79.7%) answered "no" 16.9% did not know, and only 3.3% answered "yes".

N	301								
Age (years)	Range: 18 to 25								
	Mean = 21.62 ± 1.54								
Gender	Female	Male							
	65.1%	34.9%							
Year	Preclinical	Clinical							
	42.2%	57.8%							
Intended specialty	Emergency medicine	General surgery	Med Sub-specialty	Medicine	OB-GYN	Psychiatry/neurology	Surg sub-specialty	Undecided	
	6.3%	13.6%	10.3 %	16.0%	3.3%	8.3%	11.0%	31.2%	
Have a family member that has been treated with NM?	Yes	No	I don't know						
	3.3%	79.7%	16.9%						

TABLE 1: Sociodemographic characteristics of participants

Table 2 represents the results on knowledge inventory, self-perception of knowledge, attitude, and self-perception of education toward NM. The knowledge inventory results indicate that a significant proportion of respondents do not know that NM devices are an FDA-approved treatment (173, 57.5%). The utility of NM in treating movement disorders was agreed upon by 43.2%, compared to its utility in treating psychiatric disorders (37.9%). Neurologists and neurosurgeons were identified as being involved in administering NM by 43.5% and 41.2%, respectively, while the role of psychiatrists was recognized by only 27.2%. Regarding their own perceptions of education, the majority of respondents (213, 70.8%) do not feel that they have been adequately trained about NM and its applications to medicine.

As for the attitude section, the results show that a majority of respondents did not know whether NM is associated with severe adverse effects (187, 62.1%), brain damage (175, 58.1%), or pain (179, 59.5%). Furthermore, a significant proportion of respondents were not sure whether NM is dangerous and should not be used (149, 49.5%), whether they would advise a close relative to receive NM (176, 58.5%), or whether they would undergo NM if required (163, 54.2%). Additionally, the majority were not sure if NM is often given to people who do not need it (147, 48.8%). Finally, in the self-perception of knowledge section, respondents rate their understanding of NM on a scale of 1 to 7, where 7 is the highest. The results show that most respondents (159, 46.2%) rated their understanding of NM as 1, followed by 2 (58, 19.3%), 3 (49, 16.3%), and 4 (33, 11.0%), and only a minority (22, 7.4%) rated their understanding to be 5 or higher. Overall levels of knowledge and attitude are shown in Figure 1.

Variable	Questions	Yes (%)			No (%)	I don't know (%)		
Knowledge	Is NM an FDA-approved treatment?	113 (37.5)			15 (5.0)	173 (57.5)		
	Is NM useful in treating psychiatric disorders?	114 (37.9)			34 (11.3)	153 (50.8)		
	Is NM useful in treating movement disorders?	130 (43.2)			24 (8.0)	147 (48.8)		
	Do the effects of NM last only a short while?	46 (15.3)			50 (16.6)	205 (68.1)		
	Does NM result in a permanent cure?	42 (14.0%)			70 (23.3)	189 (62.8)		
	Are psychiatrists involved in administering NM?	82 (27.2%)			41 (13.6)	178 (59.1)		
	Are neurologists involved in administering NM?	131 (43.5)			33 (11.0)	137 (45.5)		
	Are neurosurgeons involved in administering NM?	124 (41.2)			32 (10.6)	145 (48.2)		
			Improve (%)			Worsen (%)	I don't know (%)	
		Does NM often worsen or improve the psychiatric illness?	59 (19.6)			32 (10.6)	210 (69.8)	
Self-perception of education		Yes (%)			No (%)	Somewhat (%)		
	Do you feel you have been trained about NM appropriately and its applications to medicine?	24 (8.0)			213 (70.8)	64 (21.3)		
Attitude		Strongly agree (%)	Agree (%)	Neither agree nor disagree (%)	Disagree (%)	Strongly disagree (%)		
	The procedure is associated with severe adverse effects	28 (9.3)	56 (18.6)	187 (62.1)	28 (9.3)	2 (0.7)		
	The procedure is associated with brain damage	12 (4.0)	58 (19.3)	175 (58.1)	48 (15.9)	8 (2.7)		
	NM is a painful procedure	26 (8.6)	47 (15.6)	179 (59.5)	39 (13.0)	10 (3.3)		
	NM is dangerous and should not be used	15 (5.0)	35 (11.6)	149 (49.5)	80 (26.6)	22 (7.3)		
	I would advise a close relative to receive NM if recommended	34 (11.3)	71 (23.6)	176 (58.5)	14 (4.7)	6 (2.0)		
	If required, I would undergo NM	41 (13.6)	77 (25.6)	163 (54.2)	12 (4.0)	8 (2.7)		
	NM is often given to people who do not need it	17 (5.6)	29 (9.6)	147 (48.8)	53 (17.6)	55 (18.3)		
Self-perception of knowledge		1 (%)	2 (%)	3 (%)	4 (%)	5 (%)	6 (%)	7 (%)
	How would you rate your understanding of NM?	139 (46.2)	58 (19.3)	49 (16.3)	33 (11.0)	11 (3.7)	5 (1.7)	6 (2.0)

TABLE 2: Knowledge and bias inventory answers.



FIGURE 1: Participants overall knowledge and attitude levels.

Table 3 shows the association between different demographics and the level of knowledge. Regarding the academic year, although the p value does not show statistical significance ($p = 0.99$), there is a high prevalence of poor knowledge among students in both the pre-clinical and clinical years (116, 91.3%, and 159, 91.4%, respectively). The intended specialty had an influence on the knowledge level ($p = 0.01$), with emergency medicine and neurology/psychiatry among the specialties that recorded a higher level of knowledge compared to other specialties. In addition, upon asking participants whether they had a family member that had been treated with a NM device, 10 answered "yes," and 8 (80%) of them had poor levels of knowledge, while 240 answered "no", 224 (93.3%) of them had poor knowledge, and for the remaining 51 participants who did not know, 43 (84.3%) had poor knowledge, showing a significant association ($p = 0.049$).

Factors	Knowledge level			P
	Good knowledge	Poor knowledge	Total	
Gender				
Female	n	20	176	0.186
	%	10.2	89.8	
Male	n	6	99	
	%	5.7	94.3	
Academic year				
Clinical	n	15	159	0.99
	%	8.6	91.4	
Pre-Clinical	n	11	116	
	%	8.7	91.3	
Intended specialty				
Internal Medicine	n	4	44	0.01
	%	8.3	91.7	
Medical sub-specialty	n	4	27	
	%	12.9	87.1	
Neurology/ psychiatry	n	4	21	
	%	16.0	84.0	

Undecided	n	5	89	94	0.01*	
	%	5.3	94.7	100		
Emergency medicine	n	4	15	19		
	%	21.1	78.9	100		
General surgery	n	2	39	41		
	%	4.9	95.1	100		
OB-Gyn	n	1	9	10		
	%	10.0	90.0	100		
Surgical sub-specialty	n	2	31	33		
	%	6.0	94.0	100		
Do you have a family member that has been treated with a NM device						
I don't know	n	8	43	51		0.049*
	%	15.7	84.3	100		
No	n	16	224	240		
	%	6.7	93.3	100		
Yes	n	2	8	10		
	%	20.0	80.0	100		

TABLE 3: Association between levels of knowledge and sociodemographic variables.

*P-value<0.05 is statistically significant

Table 4 demonstrates the association between demographics and attitude levels. Out of a total of 196 females, only 8 (4.1%) had a good attitude towards gender, while 188 (95.9%) had a poor attitude. Among the 105 males, 17 (16.2%) had a good attitude towards gender, while 88 (83.8%) had a poor attitude. The statistical significance of the difference in attitude between males and females has a very low p-value ($p = 0.0003$), suggesting a strong association with a larger proportion of females having a poor attitude towards NM compared to males. Interestingly, preclinical students had a better level of knowledge (11.0%) compared to clinical students (6.3%). A significant association was noted between level of knowledge and having a family member that has been treated with a NM device ($p = 0.04$).

Factors	Attitude level				P
	Good attitude	Poor attitude	Total		
Gender					
Female	n	8	188	196	0.0003**
	%	4.1	95.9	100	
Male	n	17	88	105	
	%	16.2	83.8	100	
Academic year					
Clinical	n	11	163	174	0.54
	%	6.3	93.7	100	
Pre-Clinical	n	14	113	127	
	%	11.0	89.0	100	

Intended specialty						
Internal Medicine	n	5	43	48	0.94	
	%	10.4	89.6	100		
Medical sub-specialty	n	1	30	31		
	%	3.2	96.8	100		
Neurology/ psychiatry	n	2	23	25		
	%	8.0	92.0	100		
Undecided	n	4	9	94		
	%	4.3	95.7	100		
Emergency medicine	n	2	17	19		
	%	10.5	89.5	100		
General surgery	n	7	34	41		
	%	17.1	82.9	100		
OB-Gyn	n	1	9	10		
	%	10.0	90.0	100		
Surgical sub-specialty	n	3	30	33		
	%	9.1	90.9	100		
Do you have a family member that has been treated with a NM device						
I don't know	n	4	47	51		0.04*
	%	7.8	92.2	100		
No	n	18	222	240		
	%	7.5	92.5	100		
Yes	n	3	7	10		
	%	30.0	70.0	100		

TABLE 4: Association between attitudes and sociodemographic variables.

*P-value<0.05 is statistically significant

**P-value<0.01 is statistically highly significant.

Figure 2 demonstrates the disruption of students' answers to the question, "Do you feel you have been trained appropriately about NM and its applications to medicine?" Despite the absence of a significant association between clinical and pre-clinical students ($P = 0.214$), pre-clinical students showed more education satisfaction (11%) when compared to clinical students (5.7%).

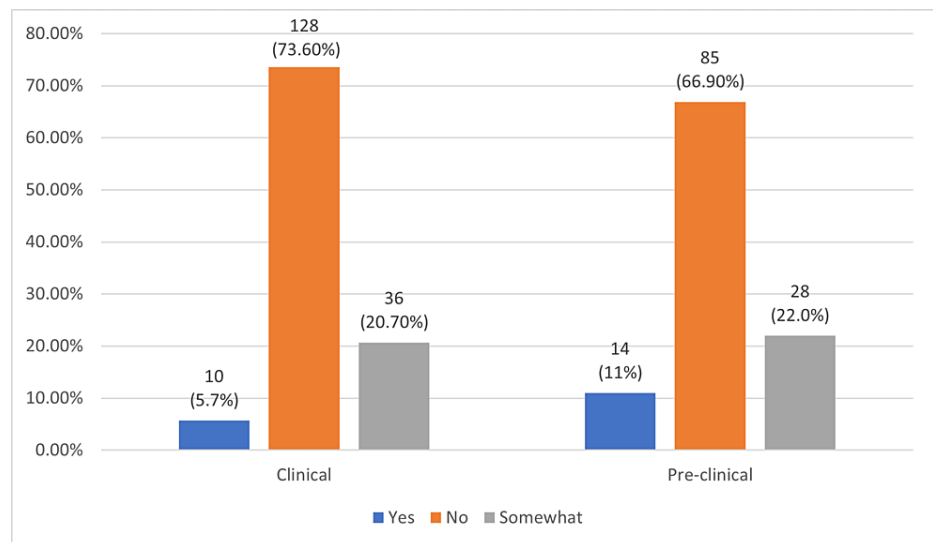


FIGURE 2: Association of self-perception of education/training with the academic year

Discussion

The current study explored the medical students' knowledge and perception of NM as a treatment modality, and a comparison was made between students in their clinical years and those in their pre-clinical years. Regardless of whether students were in the pre-clinical or clinical stages of their education, the study found that there was a significant lack of knowledge regarding the practical use of NM among the participants.

The initial assumption was that students who had more exposure to clinical settings would have higher levels of confidence and knowledge. However, the study's results contradicted this assumption. This contradiction could be indicative of both a lack of basic understanding in the classroom and insufficient practical training in NM within clinical placements.

Considering the increasing use of NM therapy, it's unlikely that physicians who specialize outside of psychiatry, neurology, or neurosurgery would have a strong understanding of the complex details, nuances, and advanced physiological principles behind NM devices. However, due to the growing popularity of this treatment, these physicians might come across patients who either need NM therapy or already have a stimulator in place. Therefore, it's important for all medical practitioners to have a basic understanding of the rationale and indications of NM devices. This knowledge is crucial for providing the best possible care for patients. However, our findings show that a significant majority of the medical students surveyed (70%) were able to identify an inadequacy of their education regarding this therapeutic approach, which is consistent with a previous study of DBS [12].

This situation highlights a significant gap in medical understanding, which is both concerning and enlightening. Even though psychiatry and neurology are major topics in medical education, it seems that NM is not adequately addressed in the current medical curriculum. It's worth noting that while 70% of students are not satisfied with the information available about NM, an unexpected 34.9% of students still felt confident in recommending NM procedures for their family members. This occurrence might potentially showcase the confidence that medical students maintain in their chosen career paths despite lacking essential foundational knowledge.

Another worrying finding is the fact that most students (57.5%) lacked awareness about the FDA-approved status of NM as a therapeutic technique, even though it has been proven effective in treating epilepsy, motor impairments, and psychiatric disorders. Additionally, it's important to mention that while 37.9% of students were aware of NM's effectiveness in treating psychiatric issues, a significant portion (62.1%) were either unsure or doubtful about psychiatrists being involved in administering DBS. Importantly, a smaller proportion of students (37.9%) believed in the potential of NM devices for alleviating psychiatric disorders. This observation is consistent with findings from a study conducted in Germany [9].

Given its current indication for treating obsessive-compulsive disorder and its potential use in other psychiatric disorders, it's crucial to address this lack of knowledge. Doing so will help future medical professionals use available treatments effectively, including NM. Regarding attitudes and biases, a small percentage of students (34.9%) expressed their readiness to suggest NM to a family member, while 39.2% were open to undergoing NM themselves if necessary. Interestingly, this differs from the results of Virginia

Tech Carilion School of Medicine, which showed an overall positive attitude with prevalence rates of 65% and 74%, respectively [12].

Moreover, our findings have shown that a considerable number (33.9%) of students believe that NM is not inherently dangerous and should be considered a viable treatment option. At the same time, a larger proportion (62.1%) are unsure about whether NM could lead to serious side effects or brain damage.

The bias inventory has shown positive results overall. Thus, it's important to highlight that the lack of sufficient information resources and perceived lack of guidance about neuromodulation among medical students aren't primarily due to a negative bias against this field. Instead, they stem from a fundamental difficulty in fully understanding the subject. This finding emphasizes the idea that including neuromodulation in the current medical education curriculum would be welcomed enthusiastically, as it has the potential to improve patient outcomes.

The knowledge, attitudes, and assumptions held by physicians wield a substantial influence over patients' choices concerning medical-surgical interventions. Consequently, the identified gaps in understanding revealed in this study highlight the need for improvements in medical education and upcoming residency training programs. These developments aim to improve physicians' comprehension of NM therapy and patient outcomes.

To address the observed knowledge and confidence gaps among medical students in relation to NM therapies, a set of comprehensive recommendations is proposed. These include enhancing medical curricula to incorporate theoretical and practical NM education, fostering collaboration with relevant specialties, prioritizing Continuing Medical Education (CME) for NM advancements, conducting public awareness initiatives, encouraging student involvement in NM research, ensuring regular updates to curriculum content, and establishing networking and mentorship opportunities. These measures collectively aim to equip future medical professionals with the necessary skills and knowledge to navigate NM therapies effectively, ensuring optimal patient outcomes and ethical decision-making.

Limitations

This study had some limitations, despite efforts to ensure accurate and representative outcomes. The use of an online questionnaire and a predominantly female respondent (65.1%) may have introduced unintended biases. It is important to consider these limitations when interpreting the results. Additionally, we adapted a previously established questionnaire for our study, making the necessary modifications for our context. However, it's important to note that, as pointed out in the original paper for this questionnaire, a standardized validation metric has not yet been developed. Nonetheless, the study provides valuable insights into the knowledge and perception of UQU medical students about NM devices and aligns with previous research. Further research is needed with diverse methodologies, exploring different sociodemographic characteristics and unexplored universities in Saudi Arabia.

Conclusions

NM is an effective treatment for several neurological disorders, including Parkinson's disease, essential tremor, dystonia, and epilepsy. As a result of the advances in research, both the number of patients being treated with this therapy and the number of physicians seeing these patients have increased. An overall lack of knowledge of NM devices was observed among medical students in this study. Hence, it is essential that all students be educated at least on the basic principles and indications for this therapy to treat patients appropriately. Other studies on the knowledge gained on this topic in other countries with different educational systems would be valuable, but unfortunately, such studies are not available. Further, it may be helpful to conduct future surveys to better understand why NM knowledge is still limited and how this could be improved, not only among medical students but also among general practitioners, neurologists, and psychiatrists. To improve the knowledge level in this field, the teaching of NM in medical schools may take various forms, including lectures, video or live observation, and in some cases, direct participation under supervision.

Additional Information

Disclosures

Human subjects: Consent was obtained or waived by all participants in this study. Biomedical Research Ethics Committee, Umm Al-Qura University. issued approval HAPO-02-K-012-2023-02-1429. Proposal Title: Knowledge and perception toward Neuromodulation Devices among medical students at Umm Al-Qura University The Biomedical Research Ethics Committee has evaluated and examined the above-mentioned research proposal and has found it to be in accordance with the specifications and conditions of the ethics of scientific research. The Committee has accordingly granted the Principal Investigator final approval concerning the ethics of scientific research Principle Investigator is permitted to: Initiate the implementation of scientific research procedures within faculty facilities and laboratories, in addition to the regional research centers and hospitals Publish in scientific journals Responsibility of Principal Investigator: Must provide a written statement to the Vice presidency of post-graduate studies and

scientific research regarding any changes in the research plan, the committee shall decide whether a new approval is needed or not. Director of Biomedical Ethics Committee Dr. Aiman M. Momenah Umm Al-Qura University. **Animal subjects:** All authors have confirmed that this study did not involve animal subjects or tissue. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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