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Pre- and Post-Clerkship Knowledge, Perceptions, and Acceptability of Electroconvulsive Therapy (ECT) in 3rd Year Medical Students

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Abstract To examine the impact of the third year psychiatry clerkship on medical students' knowledge and opinion of ECT at University of Missouri-Columbia School of Medicine. Despite overwhelming evidence of ECT's efficacy and safety for refractory affective illnesses, (among other conditions), it remains a misunderstood and underutilized intervention. Several studies indicate that ECT stigma and misinformation, unfortunately, does not spare the medical community. Medical students are an optimal group to study, as they are forming their perspectives on different specialties. Few studies have measured the effect of education programs (e.g., clerkships, lectures, observation of ECT) on medical students' perspectives on ECT.

Keywords Electroconvulsive therapy · Medical students · Stigma · Clerkship

Introduction

Electroconvulsive therapy (ECT) remains a highly effective treatment for refractory affective illnesses, psychotic depression, Catatonia, among several other psychiatric and medical conditions. The STAR*D report, one of the largest clinical trials of antidepressant medications,

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found only 67% of depressed patients achieved full remission, while remission rates of 83-95% have been reported with ECT [1]. A recent study using data from the Texas Department of State Health Services from over 166, 000 ECT treatments reported a mortality rate of 2.4 per 100,000 treatments within 1 day and 18 per 100,000 within 14 days. The later rate did not account for causality or association and likely over estimates the death rate [2]. The mortality rate of ECT, following an analysis of the data regarding adverse events provided by the Texas Department of Mental Health, was determined to be 2 to 10 in 100,000, similar to the rate for anesthesia alone, which is 3.4 per 100,000 [3]. However, in spite of the overwhelming evidence of ECT's efficacy and safety, it remains a misunderstood and often underutilized therapeutic intervention. Studies of the public's perception of ECT have remained negative, for example only 1.2% of those surveyed in Switzerland were in favor of ECT [4, 5]. In their recent study on eligibility for deep brain stimulation (DBS), Filkowski and colleagues presented insights of effects of stigmatization on medical decision making as a significant number of study volunteers were excluded from DBS as they had not received prior adequate ECT and were more willing to receive experimental brain surgery [6]. ECT misinformation and stigma, unfortunately, does not spare the medical community. Forty percent of the medical students in one study believed that ECT is frequently misused, and around 31% believed the procedure was used to punish violent or uncooperative patients [7]. Despite ECT's proven safety, 50% of medical students described ECT to be dangerous and 32% thought it could cause permanent brain damage [8]. Several studies have reported similar negative opinions and falsehoods about the procedure, perhaps as the source of information regarding ECT is often obtained from cinematic presentations that may have an outdated and misrepresented depiction, leading to these negative perceptions [9]. In one study of 165 medical students in India mass media had the largest contribution on opinions and knowledge about ECT [10]. In fact one study that surveyed pre- and post-cinematic exposures to ECT negatively influenced medical students' support for the procedure and may lead them to dissuade family members from receiving ECT [11]. Several studies in the last 10–15 years have investigated medical students' knowledge and perception about electroconvulsive therapy. These include papers studying medical students in Greece, Nigeria, Thailand, UK, Egypt, Iraq, India, Turkey, Ireland, Australia, as well as the United States (University of Texas, Loma Linda University, University of Arkansas, Jefferson Medical College, and UCSF). One study showed that direct participation or observation of ECT had a significant positive impact on the post-psychiatry clerkship opinions of medical students regarding ECT [12]. The purpose of our study was to investigate the impact of the third year psychiatry clerkship on the opinions and knowledge of medical students regarding ECT.

Design/Methods

We sought and received institutional review board approval for our study protocol. Written permission was obtained from the primary contact/author McFarquahar, et al. to administer a modified version of their 23-question survey. All 3rd year medical students at the University Missouri-Columbia School of Medicine from February 2015 to May 2016 were invited to complete our 25-item Likert scale survey prior to and at the end of their psychiatry clerkship [9]. Students were allowed to decline participation aka "opt out." The survey was administered by and collected by a 3rd party, not the researchers. Data was de-identified and secured on private server. All statistical analyses were calculated using SAS 9.4 (SAS Inc.,

Cary, NC). The threshold for statistical significance was set at 0.05. Paired T test and chisquared test were used to evaluate for significant differences over the clerkship. Demographic data were collected and questions 20, 21, and 25 were analyzed separately as they used a different scale and/or were descriptive data.

Results

79 of 133 3rd year medical students completed the pre- and post-clerkship survey and were included in the data analysis (59% response rate). Information was gathered regarding where medical students learned about ECT. Prior to clerkship, 94% (n = 74) of students reported learning about ECT from either cinema/television or word of mouth (40 [51%] and 34 [43%] students respectively). While 67% (n = 53) endorsed acquiring information about ECT from a course of lecture. There was little pre-clerkship exposure to ECT as only 3 medical students, or just fewer than 4%, reported a history of witnessing or observing ECT. One student did not respond and 6 (around 7%) stated they have no prior knowledge of ECT. (See Table 1).

Demographic data including age, gender, religion, first choice of specialization and political leaning was requested at the bottom of the questionnaire. The sample included 45 men and 34 women; the mean age was 26.27 years (SD 4.14), and the mean political leaning was 2.90 (1–5) (higher numbers indicating conservative political philosophy) (SD 1.26). Specialty was reported as general practice (Family Medicine, Internal Medicine, Medicine, Pediatrics, Primary Care, n = 24, 30.38%), surgery/surgical subspecialties (Surgery, Acute Care Surgery, ENT, Neurosurgery, Orthopedics, Plastic Surgery, Urology, OB/GYN, n = 21, 26.58%), specialty (Anesthesia, Dermatology, Emergency Medicine, Heme-Onc, Neurology, Ophthalmology, Pathology, Physical Med and Rehab, Radiology, n = 19, 24.05%), undecided (including N/A) (n = 12, 15.19%), and psychiatry (n = 3, 3.80%). Religion was grouped as Christianity (n = 35, 44.30%), Atheist/None (n = 23, 29.11%), Catholic (n = 15, 18.99%), and other religions (Hindu, Jewish, Muslim) (n = 6, 7.59%).

We performed a *paired t-test* to evaluate for significant differences between student beliefs and knowledge of ECT pre- and post-clerkship. Table 2 summarizes the descriptive statistics for the scores of each question. All but 4 questions demonstrated a significant improvement in the knowledge and beliefs of ECT after the clerkship. Only questions 2 (whether ECT is performed in the U.S.), 6 (whether psychiatrists understand how ECT works), 15 (whether ECT can affect the ability to think/reason for >6 months), and 16 (whether ECT causes

Source	Number of responses		
Course or lecture	53		
Cinema/TV	40		
Word of mouth	34		
Profession publications	15		
Newspapers/magazines	7		
Personal experience	7		
No Knowledge	6		
Witnessed (Observed) ECT	3		
Other ("medical student" "psychiatrist")	2		
No response	1		

Table 1 Pre-clerkship sources of opinions/knowledge of ECT (multiple responses allowed)

Question number	Pre clerkship, mean	Pre clerkship, SD	Post clerkship, mean	Post clerkship, SD	Df	t ^b	p-value ^c
1	3.42	0.79	3.85	1.13	78	2.95	0.0042**
2	4.86	0.38	4.95	0.27	78	1.83	0.0704
3	4.74	0.52	4.95	0.32	77	3.34	0.0013**
4	3.58	0.74	4.32	0.61	78	7.24	<.0001****
5	3.16	0.65	3.59	0.81	78	4.06	0.0001***
6	3.53	0.86	3.59	1.02	77	0.52	0.6073
7	4.05	0.71	4.58	0.76	78	5.50	<.0001****
8	4.68	0.52	4.96	0.25	78	4.90	<.0001****
9	4.75	0.54	4.95	0.27	78	4.14	<.0001****
10	4.08	0.78	4.68	0.63	78	6.33	<.0001****
11	3.97	0.96	4.70	0.70	78	6.50	<.0001****
12	3.94	0.98	4.78	0.61	78	7.34	<.0001****
13	3.48	0.89	4.65	0.83	78	9.59	<.0001****
14	3.20	0.70	3.99	0.97	78	6.24	<.0001****
15	3.41	0.76	3.38	1.05	78	-0.21	0.8308
16	2.58	0.69	2.71	1.12	78	0.94	0.3480
17	3.27	0.76	3.78	0.86	78	5.36	<.0001****
18	4.37	0.60	4.81	0.46	78	6.63	<.0001****
19	2.43	1.05	3.18	1.33	78	4.97	<.0001****
22	3.84	0.63	4.39	0.63	78	6.96	<.0001****
23	3.57	0.76	4.35	0.72	78	7.74	<.0001****
24 a	3.47	1.29	3.32	1.38	76	-1.54	0.1283
24 b	2.48	1.08	2.16	1.24	75	-3.11	0.0027**
24 ^c	4.46	0.57	4.43	0.72	76	-0.17	0.8631
24 d	4.22	0.83	4.26	0.93	76	0.29	0.7749
24 ^e	3.73	0.93	3.94	0.98	76	1.45	0.1500
24 [_] f	4.19	0.85	4.44	0.77	77	2.97	0.0040**
24_g	3.10	0.83	3.83	0.95	77	5.63	<.0001****

Table 2 (modified Likert scale^a). Belief and knowledge about ECT by individual questions

^a # 4, 7, 8, 9, 10, 11, 14, 15, 17, 18 are all negative (meaning absolutely not is the "correct" or expected answer) ^b t-value of testing the difference between before and after clerkship (difference = post-pre)

^c *: *p*-value<.05, **: p-value<.01, ***: p-value<.001, ****: p-value<.001

memory loss for events weeks prior to the procedure) showed no significant change over the rotation. Questions 24a-24f evaluated medical students' willingness to try various non-ECT approaches or treatments to address severe depression. Only question 24b and question 24f and 24 g showed a significant difference over the rotation, with students reporting to be less likely to consider using homeopathy and more likely to take antidepressant medication after the clerkship.

To further investigate general trends in students' knowledge and perception of ECT, survey questions were grouped by topic and re-analyzed via Paired T-test. The topics tested included: "indications" (questions 1–3, 9, 19), "mechanism of action" (questions 6–8, 11, 13), "procedure" (questions 12, 14, 18), "effectiveness" (question 4), risks/side effects (questions 5, 10, 15–17), "impression/opinion of ECT" (questions 22, 23, 24 g), and "opinions of other treatments" (Questions 24a-f). All topics, with the exception of "opinions of other treatments," demonstrated a significant change pre- and post-rotation with improvements in both understanding and perception of the procedure (Table 3).

Question 20 asked those surveyed to choose an adjective to describe their overall feeling of either receiving ECT or having a close contact receive ECT, ranging from "terrified" to "not worried." After the clerkship medical students had a significant improvement in their

	Pre Clerkship, mean (SD)	Post Clerkship, mean (SD)	Difference, mean (SD)	t- value	p-value ^a
Indications	4.04 (.33)	4.37 (.38)	.33 (.36)	7.95	<.0001****
Mechanism of Action	3.94 (.42)	4.49 (.42)	.55 (.48)	10.16	<.0001****
Procedure	3.84 (.49)	4.53 (.46)	.69 (.59)	10.40	<.0001****
Effectiveness	3.58 (.74)	4.32 (.61)	.73 (.90)	7.24	<.0001****
Risks/Side effects	3.30 (.32)	3.63 (.40)	.33 (.44)	6.75	<.0001****
Impression/Opinion of ECT	3.50 (.53)	4.19 (.59)	.69 (.69)	8.80	<.0001****
Opinions of other treatments	3.76 (.56)	3.76 (.65)	.01 (.49)	.12	.9063

Table 3 (modified Likert scale). Belief and knowledge about ECT by grouped questions

^a *: p-value<.05, **: p-value<.01, ***: p-value<.001, ****: p-value<.001

perceptions of ECT ($\chi 2 = 33.00$, df = 6, *p*-value<.0001). Before clerkship, one participant out of 79 expressed the overall feeling about having ECT him/herself terrified. 24.05% (*n* = 19) said they are anxious or fearful, 51.90% (*n* = 41) felt slightly uncomfortable, and only 22.78% (*n* = 18) said they are not worried. After clerkship, none of them said they would terrified and more than half (55.70% (*n* = 44)) said they are not worried and 41.77% (*n* = 33) expressed they are slightly uncomfortable. Only 2.53% (*n* = 2) said they are anxious or fearful. Figure 1 illustrates the number of students' selections pre- and post-clerkship. Students were much more likely to probably or definitely consider ECT after their rotation Fig. 2.

Students were furthermore asked to describe their apprehensions about ECT by selecting from several multiple choice options (question 21, multiple answers were allowed). Before the



Frequencies of Overall Feeling About Having ECT (Question 20)

Fig. 1 Frequencies of overall feeling about having ECT (Question 20)



Frequencies of Considering ECT for Depression (Question 24g)

Fig. 2 Frequencies of considering ECT for depression (Question 24 g)

clerkship, they were most concerned about not knowing what can happen with ECT (52 selections or 66% of students), discomfort with the idea of having a seizure (40 selections or 51% of students), and about the possibility of pain with the procedure (36 selections or 45% of students). Although a significant number continued to rate discomfort with the prospect of having a seizure (38 selections or 48% of students), the most common concerns post fellowship were regarding memory loss (40 selections or 51% of students) and the possibility of brain damage (23 selections or 29% of students). Cochran-Mantel-Haenszel (Chi Sq. w/3 variables) statistics were calculated and there was no association between the overall feeling about having ECT (question 20) and the choice of specialty before clerkship ($\chi 2 = 2.35$, pvalue = .6711) and after clerkship ($\chi 2 = 1.99$, *p*-value = .7371), religious affiliation before clerkship ($\chi 2 = 6.12$, p-value = .1057) and after clerkship ($\chi 2 = 0.40$, p-value = .9397), age (those 25 or younger (n = 45) vs. those 26 or older (n = 34)) before clerkship $(\chi 2 = 0.008, p - 1)$ value = .9272) and after clerkship ($\chi 2 = 0.001$, *p*-value = .9750), and political persuasion before clerkship ($\chi 2 = 1.75$, p-value = .4168) and after clerkship ($\chi 2 = 1.36$, p-value = .5073). There was a statistically significant difference after clerkship with gender, (df = 1, χ^2 = 6.2812, p-value = .0122); male participants had more improvement of the overall feeling after the clerkship (df = 6, $\chi 2 = 20.3333$, p-value = .0024) than that female participants (df = 6, $\chi 2 =$ 13.0303, p-value = .0426) (Table 4).

In a subgroup analysis, our group analyzed for significant differences from the postclerkship survey results between the students reporting they witnessed "live" ECT (n = 41) from those who did not (n = 38). Students who attended ECT treatment(s) had a significantly more correct understanding of the procedure (mean 4.64 vs. 4.40, p < .05) and mechanism of action (mean 4.60 vs. 4.38, p < .05). The two groups did not differ significantly in their

Table 4 Frequency table of Question 21 (multiple responses are allowed)	Category Pre Clerkship		Post Clerkship	
allowed)	а	26	40	
	b	32	23	
	с	36	9	
	d	5	1	
	e	19	10	
	f	40	38	
	g	11	18	
	ĥ	52	17	
	i	14	7	
	i	4	3	

knowledge of indications, effectiveness, safety (risks/side effects) or opinions of other treatments (Table 5). There was not a statistically significant difference when questions regarding impressions/opinions were grouped (Table 7). However, when we analyzed medical students' overall feeling about being an ECT patient or having a close friend or relative have ECT (question 20), those who observed ECT had a significantly more positive perception of the procedure ($\chi 2 = 8.02$, *p*-value = .0181) (Table 6). 70.73% of ECT observers described themselves being "not worried" about having ECT performed on themselves (or close contacts) vs. only 39.47% of students who did not observe ECT. Figure 3 illustrates the frequencies of each opinion in this subgroup analysis, showing a more positive impression of ECT in the observer group. Interestingly, although the ECT observers were more comfortable with ECT, the ECT non-observers were no less likely to consider it as a treatment option if they were severely depressed (question 24) ($\chi 2 = .0783$, *p*-value = .7796, Table 7).

Discussion

Lecture, video series, or live (observed) ECT may help improve both ECT knowledge and perception, which has been demonstrated in some studies [13]. Several researchers suggest that people who have more knowledge regarding the procedure have more positive feelings towards ECT, with a few exceptions [14]. Shah, et al. reported that medical students had improved knowledge and more positive opinion of ECT after a required ECT lectures over the clerkship, and those that had also observed ECT sessions during the clerkship had *a more* positive response than their peers [15]. Although it appears observing *unmodified* ECT (as opposed to modified) does not improve students' acceptability of the procedure [16].

Table 5	Comparisons of	f ECT ol	bservers vs	s. non-observers	on post	clerkship)	(independent	t-test)
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	ECT observers, mean (SD)	ECT non-observers, mean (SD)	t-value	p-value
Indications	4.41 (.31)	4.33 (.16)	95	.3461
Mechanism of Action	4.60 (.34)	4.38 (.47)	-2.28	.0255*
Procedure	4.64 (.38)	4.40 (.51)	-2.38	.0196*
Effectiveness	4.32 (.61)	4.32 (.62)	01	.9926
Risks/Side effects	3.65 (.35)	3.61 (.46)	42	.6759
Impression/Opinion of ECT	4.28 (.56)	4.08 (.61)	-1.53	.1291
Opinions of other treatments	3.65 (.61)	3.88 (.67)	1.59	.1167

Bold entries represents statistical significance

Post Clerkship		Question 20					
		Anxious or Fearful	Slightly uncomfortable	Not worried	Total		
ECT non- observer	Frequency	1	22	15	38		
	Overall $\%$ (total = 79)	1.27%	27.85%	18.99%			
	Row $\%$ (total = 38)	2.63%	57.89%	39.47%			
ECT Observer	Frequency	1	11	29	41		
	Overall $\%$ (total = 79)	1.27%	13.92%	36.71%			
	Row $\%$ (total = 41)	2.44%	26.83%	70.73%			
Total		2	33	44	79		

Table 6Frequency Table of Question 20 between ECT observers and ECT non-observers after clerkship (ChiSq.)

Interestingly many film and television scenes present *unmodified* ECT [17]. The latter of which may, at least in part, contribute to stigma of the procedure. Previous studies surveying medical students' opinion of unmodified ECT suggested that medical student's may have more negative opinion of the procedure [17, 18].

Medical students' understanding and favorability may be greater than that of nursing students, as Byrne et al. presents in his study of Irish health students and physicians. The nursing students did not demonstrate improved opinions of ECT after observation. Furthermore, the nursing group overestimated mortality rates and most did not know if ECT caused brain damage and only 1 psychiatric nurse had a positive attitude of the procedure [19]. The authors argue that this discrepancy in the nursing population could affect valid informed consent [19].



Post-rotation frequencies of question 20 between ECT Observers and Non-Observers

Fig. 3 Post-rotation frequencies of question 20 between ECT observers and non-observers

Post clerkship		Question 24_g						
		Absolutely not	Probably not	Not sure	Probably	Definitely	Total	
ECT	Frequency	0	4	7	16	10	37	
non-observer	Overall $\%$ (total = 78)	0.00%	5.13%	8.97%	20.51%	12.82%		
	Row % (total = 37)	0.00%	10.81%	18.92%	43.24%	27.03%		
ECT Observer	Frequency	1	4	5	23	8	41	
	Overall $\%$ (total = 78)	1.28%	5.13%	6.41%	29.49%	10.26%		
	Row $\%$ (total = 41)	2.44%	9.76%	12.20%	56.10%	19.51%		
Total	. ,	1	8	12	39	18	78	

Table 7 Frequency Table of Question 24_g between ECT observers and ECT non-observers after clerkship (Chi Sq.)

Another study demonstrated statistically-significant positive effects on knowledge and attitudes towards ECT in medical students exposed to "live" ECT or videotape, suggesting either live or recorded demonstrations may be effective interventions [13]. Unlike findings from Warnell, et al. we found that observing ECT, in fact, significantly improves medical student's opinions of ECT and makes them more likely recommend the procedure compared to their counterparts who only watched an instructional video and had a lecture. In addition our data suggests that observers of ECT had a better understanding of the mechanism of action of the intervention.

Our students were exposed to a one-hour lecture (including the indications, risks/side effects, benefits, etc.) and short video of the ECT procedure itself.

As above, Shah as well as our data, suggest that there is significant improvements in perceptions and knowledge of ECT post-clerkship after medical students rotate on psychiatry and have a required didactic on the subject. It appears that even one lecture, such as the 90 min didactic reported by Papakosta, et al., may be beneficial in increasing favorable opinions of ECT in medical students [20]. Although the authors argue that such a positive perception may or may not be enduring, it does provide encouragement for the importance of didactics for training programs that lack ECT infrastructure. Benefits of documentary-style video tape of ECT as discussed by Warnell and colleagues could serve to complement lectures and clinical teaching on the psychiatry rotation.

67% (*n* = 53) of our group reported having had a lecture regarding the procedure prior to starting the rotation, suggesting that at baseline the medical students who completed the surveys were fairly educated about the procedure prior to the clerkship.

Trenton and colleagues found that there is not a significant difference of opinion in medical students who observe vs. participate in ECT [12].

Just over half of our sample reported having viewed cinematic or television portrayals of ECT. Unfortunately, there appears to be a trend in recent years that cinematic representations of this potentially life-saving procedure are becoming progressively negative [5]. A more recent international study reviewing 52 films, 21 television programs, and 2 animated sitcoms suggests that ECT is used as "a metaphor for repression, mind and behavior control" with 80.7% of films and 72% of television programs showing a negative and inaccurate picture of the procedure [17]. This highlights the importance of educating the public and medical community more than ever as Walter et al. demonstrated that one-third of medical students decreased their support of and nearly 25% would dissuade a close contact from ECT after viewing cinematic representations of the intervention [11].

To our knowledge our study is one of only 5 investigating pre- and post-education's effects on ECT understanding and perception in medical students. More studies are needed to further investigate the importance of educational interventions. Exposure to ECT, whether through education during the psychiatry clerkship or via direct observation, improves medical students' knowledge of and attitudes toward ECT. As previous studies have suggested, direct observation of *modified* ECT promotes the most positive opinions of ECT. Our study adds to a growing body of literature supporting the inclusion of ECT education into medical students' curriculum.

As Choy and colleagues argue, journalists have a duty to help correct public misperception of ECT. A recent editorial highlights the important role that news media also plays in public perception. Despite 75 % of patients responding well and having a positive perception of the procedure, journalists often give equal consideration to positive ECT stories and unsubstantiated negative portrayals, which risks equating a more likely positive experiences with an unlikely negative one [21].

And most recently Pranjkovic reported data from 190 medical students in Croatia, demonstrating that the psychiatric clerkship increases acceptance of ECT and that observing modified ECT more positively imbues positive opinion and knowledge of ECT [18].

There may be cultural factors that affect medical student's perceptions of ECT. In their transcultural study of Iraqi, Egyptian, and British medical students, Abbas and colleagues found that while theoretical knowledge base was best in Iraqi medical students, the UK medical students showed the most positive attitudes of the procedure, and only 3.5% of the Egyptian students observed ECT in their training. They argue to a specific lecture and observed ECT may help promote the procedure across all three groups [22]. It is important to remember that some developing countries may still employ unmodified techniques for ECT due to decreased access to anesthesia, which does not appear to improve medical student's acceptability ECT [16].

Our study's limitations include a relatively small sample size and response rate, which could reduce generalizability. Some students voluntarily decided to observe ECT. It is possible that there are several layers of selection bias. Students that elected to complete the pre- and post-clerkship survey may hold the procedure in high or low esteem. For instance the 41%, who did not may have a lower regard for ECT. We attempted to encourage more responses by keeping surveys anonymous. Additionally, the students who chose to observe ECT may have had a higher opinion or interest of/in the intervention than those who did not, which could have influenced the survey results.

Clothier and colleagues reported that medical students who rated themselves as highly knowledgeable about psychiatric pathology had a greater bias against ECT [7]. Another study also found that medical students who reported having superior knowledge of psychiatry had a more negative opinion of ECT compared to peers [8].

Future studies may explore if there are gender differences in ECT acceptability, as we found. In Gazdag's 2005 study of Hungarian medical students, female students had a significantly more negative attitude towards ECT and encompassed a higher proportion of medical students who would refuse to be treated with ECT [8].

Conclusion

Our study demonstrates that exposure to ECT, whether through education during the psychiatry clerkship or via direct observation, improves medical students' knowledge of and attitudes toward ECT. As previous studies have shown, our study also suggested that direct observation promotes the most positive opinions of ECT. We join the growing number of authors calling for all medical students to have didactics and mandatory observed sessions of modified ECT; which has been demonstrated to promote positive opinions of ECT.

Compliance with Ethical Standards All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Conflict of Interest The authors declare that they have no conflict of interest.

Ethical Approval In case animals were involved: This article does not contain any studies with animals performed by any of the authors.

In case humans are involved: Informed consent; All individual participants included in the study were provided an "Opt out" form to decline participation.

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