



The Effects of Mobile Learning and Group Discussion for Psychotropic Drug Education on Nursing Students' Learning, Satisfaction, and Attitude: An Educational Intervention

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Abstract

Background: Familiarity with and management of drug side effects is among nurses' main educational needs with respect to pharmacological care in psychiatry departments.

Objectives: This study aimed to determine the effects of psychotropic drug education through mobile learning and group discussion on nursing students' learning, satisfaction, and attitude.

Methods: This educational intervention was done at EbneSina Psychiatric Hospital, affiliated with Shiraz University of Medical Sciences, in 2018. A total of 28 students were randomly divided into 2 groups, each containing 16 and 12 subjects. The first group underwent the educational intervention through mobile learning. The second group received the educational intervention through group discussion. The students' learning and satisfaction were assessed and compared before and 2 weeks after the intervention. Attitudes were also assessed within the mobile learning group. Data were analyzed using paired and independent sample *t*-tests.

Results: The results revealed a significant difference in satisfaction between the 2 groups after the intervention (38.69 ± 4.78 in the mobile learning group vs 33.13 ± 5.51 in the discussion group; $P = 0.02$). However, no significant difference was found after adjustment for baseline, age, and sex. The results also indicated that the students in the mobile learning group developed a significantly more positive attitude after the intervention compared to the baseline ($P = 0.038$).

Conclusions: The study findings indicated that the utilization of smartphones for learning about psychotropic drug management in psychiatric departments might be effective in enhancing student's learning outcomes, satisfaction, and attitude. Thus, further studies with larger sample sizes are recommended to be conducted on other medical and nursing apprenticeships.

Keywords: Mobile Learning, Group Discussion, Psychotropic Drugs

1. Background

Clinical education is an essential and integral component of medical sciences education. It plays a fundamental role in training individuals to become proficient and competent healthcare professionals (1). Nursing students spend a considerable part of their course of education in clinical wards. Thus, the evaluation of clinical education is considered to be the basis of educational planning in nursing schools (2). Identification

of effective factors in clinical skills learning is effective in the reduction of problems and empowerment of positive points. In this regard, students themselves are the best sources for evaluation since they are in direct contact with the process (3). Clinical skills should be learned in a way that is accompanied by the highest quality and accuracy, eventually increasing patients' physical safety and trust. Hence, possessing sufficient knowledge and skills is highly essential for professional nurses. Evidence has also indicated that the common curricula have not provided

students and nurses with the opportunity to improve their medication management skills (4). Students have also pointed out their weaknesses in pharmacology courses (5).

In psychiatry departments, the goal of drug therapy in mental patients is to try to moderate or reduce pathological behaviors, thoughts, and moods. These drugs directly affect a person's behavior and performance. Each category of psychiatric drugs has other uses in addition to the main use (6, 7). Therefore, due to the increasing complexity and wide range of treatment options of these drugs, the treatment team must be aware of potential side effects, drug interactions, and how to treat unwanted consequences. Considering the unpredictability of drug responses, the frequent occurrence of side effects, and patients' doubts about taking drugs, a strong relationship between the treatment team and the patient is needed (8). Therefore, paying attention to the educational needs of nurses working in psychiatry departments is an effective and important step in improving their abilities. Familiarity with and management of drug side effects are among nurses' main educational needs with respect to pharmacological care in psychiatry departments (9).

In these departments, pharmacological treatment aims to modify or reduce pathological behaviors, thoughts, and moods in patients with mental disorders. Such medications affect individuals' behaviors and functions directly (10). Generally, educational goals can be achieved via the use of appropriate instruction techniques (11). In fact, the selection of a proper instructional method can play a critical role in learners' skill learning and changing their attitudes (12). Traditional educational methods often promoted passive learning, neglecting the individual differences and needs of learners and placing less emphasis on problem-solving, critical thinking, and other high-level cognitive skills. Therefore, many experts have pointed to the necessity to modify or complement the traditional educational methods (13). The World Federation for Medical Education has developed standards for medical education, advising universities of medical sciences to encourage students to take active roles in the teaching-learning process and prepare them for continuous learning (14). In this context, novel educational methods have to be inevitably used in medical sciences instruction (15), and nursing education should also be compatible with these changes (16).

Education via group discussion is among such models, which provides the ground for learners to discuss issues with each other, as well as with their instructor, to exchange information, thoughts, and ideas and solve problems (17).

Group discussion as a modern pedagogical technology

has a potential effect on teaching through its effect on the content of education, decisions that link education to life, and so on. It increases students' attitudes and enthusiasm for learning, revealing their hidden abilities and talents. In addition to the advantages of this method, it has some shortages. For instance, the ability to monitor students is low, negative competition is common, and mutual conflict may happen. However, these shortages can be controlled by teachers (18).

Electronic learning is another novel technology-based educational method using computers, the internet, web pages, satellite applications, multimedia, virtual education, computer simulations, and mobile phones (16, 19). Specification of mobile phones when used as learning technology, such as continuity in the learning process, availability to nearly all academic learners, learner-centeredness, flexibility, interactions, and so on, gives it the potential opportunity to be used in the teaching-learning process (20). On the other hand, studies have shown some challenges in front of accepting mobile learning, such as lack of research evidence on their effectiveness, lack of efficient models, resistance of teachers, difficulty connecting to printers, limited screen size, difficulty in navigating web pages, and other obstacles related to speed, storage, battery life, and infrastructure (18).

2. Objectives

The primary objective of the present study was to examine the effects of mobile learning and group discussion on nursing students' learning outcomes in psychiatric wards, specifically focusing on psychotropic drug management education. The secondary objectives were to assess the students' satisfaction and attitude toward this educational approach.

3. Methods

3.1. Study Design and Setting

This educational intervention study utilized a pretest/posttest design and took place at EbneSina Psychiatric Hospital, which is affiliated with Shiraz University of Medical Sciences. The study was conducted between February and July 2018 and was performed in accordance with the ethical guidelines established by the ethical committee, with the assigned code 95-01-08-13957.

3.2. Sample Size

The G-Power software version 3.1 was used to calculate the sample size. According to a satisfaction variable (mean [SD]₁ = 115.56 [17.57] and mean [SD]₂ = 132.24 [17.92]) in a previous study (21) and considering $\alpha = 0.05$, power = 80%, and *t*-test for differences between the 2 independent groups' mean, a large effect size, 2-tailed P value, and 1:1 allocation ratio, a 28-subject sample size was determined for the study.

3.3. Participants

Inclusion criteria were being involved in education at the time of the study, having passed the theoretical courses of pharmacology and mental health prior to the study, being involved in mental health apprenticeship at the time of the study, being willing to cooperate in the study, and signing written informed consent. Exclusion criteria were not taking part in group discussion sessions. Students who did not have Android-based phone systems were unable to install the software and, consequently, were excluded from the study group.

From 40 students who had taken mental health apprenticeships in psychiatry wards, 28 students met the inclusion criteria and were assigned to 2 groups of 16 and 12 students in mobile learning (intervention group) and discussion (control group), respectively, using simple randomization and the table of random numbers (Figure 1).

To conceal randomization, 28 opaque envelopes were numbered and given to the research assistant. Each envelope was opened at the time of the students' visit and was used to assign the subject to pre-defined groups. All students in both groups were completely blinded to the group allocations, including the research assistant, who divided the participants into groups based on the envelope numbers, and the researchers who filled out the questionnaires.

3.4. Instruments

The study data were collected using a demographic information form, Students Learning Scale, a questionnaire evaluating nursing students' satisfaction, and a questionnaire assessing the students' attitude toward mobile learning with the instruction methods. The demographic information form included age, sex, marital status, living place, educational semester, previous semesters' average points, type of mobile phone, membership in social groups, membership in scientific websites, and methods of access to course questions. The Students Learning Scale was designed by researchers with 20 items according to the main

goals of the learning questionnaire assessing the rate of learning of psychotropic drugs, including antipsychotics, anti-anxiety drugs, antidepressants, and mood stabilizers. Each question had one score, and the total was 20. The face validity of this questionnaire was assessed by 5 experts. The reliability of this questionnaire was assessed in a random sample, and Cronbach's alpha was 0.75.

The questionnaire assessing the students' attitude toward mobile learning was designed by Naderi et al in the form of a test containing 13 items. The items were responded using a 5-point Likert scale with the following options: Completely agree (5), agree (4), no idea (3), disagree (2), and completely disagree (1). The reliability of the questionnaire was approved by Cronbach's alpha = 0.90. Additionally, its validity was confirmed by factor analysis (22).

The students' satisfaction with the instruction methods was evaluated using a questionnaire consisting of 16 items responded through a 3-3-point Likert scale (completely, to some extent, never), ranging from 1 to 3. Thus, the minimum and maximum scores of the questionnaire were 16 and 48, respectively. The face and content validity of the questionnaire were assessed by 15 experts using Waltz and Bausell's index, and the required modifications were applied. Accordingly, the content validity index was 0.85. Moreover, the reliability of the questionnaire was found to be 0.9 using the test-retest method (23).

3.5. Interventions

After obtaining approval for the research proposal from both the University's Research Vice-Chancellor and the Ethics Committee, the researcher initiated the process of gathering the necessary content by conducting searches in library resources and reviewing relevant articles. The next stage involved the preparation of the educational content, which included information about different categories of psychotropic drugs, pharmacology, pharmacokinetics, pharmacodynamics, clinical pharmacology, drug toxicity complications, names of different drug categories, nursing care, and advisable points. After preparing and designing the educational content and gaining the approval of the research team, the researcher referred to the Virtual School (Comprehensive Center of Excellence for Electronic Learning in Medical Sciences) at Shiraz University of Medical Sciences to develop and evaluate the e-content based on instructional design standards and constructivism theory. This theory states that learning is a process based on knowledge and constructed on learners' experience (24).

The prepared software included sounds, images, movies, animations, text files, searchability, chat room,

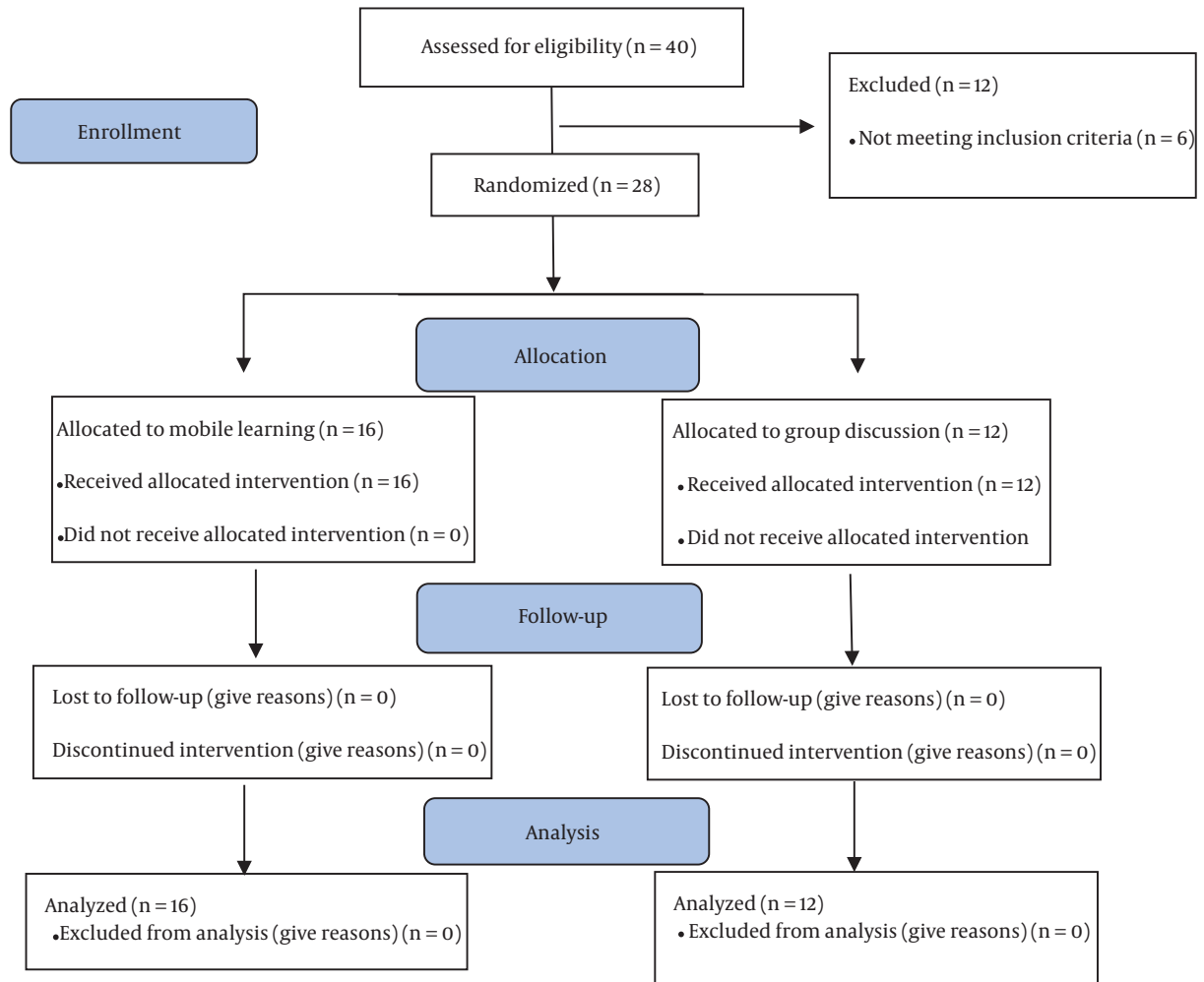


Figure 1. The flowchart of the study

and a final exam at the end of each drug category. The students observed 8 icons on the software's homepage and could have access to the materials by clicking on each icon. It should be noted that the final exam icon could not be run until the end of the course.

After all, the educational software was organized into 5 main sections, namely antidepressants, mood stabilizers, antipsychotics, anti-anxiety drugs, and summary. Each section consisted of subsidiary divisions, including the drug category's basic and clinical pharmacology, pharmacokinetics and pharmacodynamics, side effects, drug interactions, drug toxicity, and nursing care and advice while receiving medications. The advantages of this software included the possibility to use the audio or written file based on the students' desire at the time of

learning, existence of images related to drug shapes and doses to make the students visually familiar with different types of psychotropic drugs, and existence of animations and videos regarding drug side effects to facilitate the students' learning of theoretical concepts. The primary content was the same in the discussion group but with different strategies. The students first got acquainted with the method during a session, and then, according to the specified schedule, the students had a group discussion and exchange of views on different categories of medicine during 6 sessions of 45 min in the hospital where the internship took place. The researcher held and managed the meetings regularly. To communicate with students and resolve issues, the researcher formed a group on social media where students could ask their questions.

The researcher asked a series of questions about the content given after each session. In the last session, all drug groups were reviewed.

To avoid information exchange (contamination bias), educational interventions were conducted in each group with a specific time interval. In so doing, first, group discussion sessions were held. A week after the end of the intervention and the related assessments, the educational intervention using mobile phones was started. In this group, the software, including the educational content, was installed on the students' Android mobile phones, and the students received the content for 2 weeks. If students had any questions, they would communicate with the researcher through a social network platform.

The 2 groups' learning and satisfaction with the instruction methods were assessed before and 2 weeks after the educational intervention. The second group was also required to fill out the questionnaire evaluating attitudes toward mobile learning before and after the intervention.

3.6. Statistical Methods

Data were entered into SPSS version 16. The qualitative and quantitative data were reported as frequency (percentage) and mean \pm SD, respectively. Furthermore, differences between and within groups were compared using independent sample *t*-test and paired *t*-test, respectively. Adjustment for baseline values and age and sex was conducted using analysis of covariance (ANCOVA). Because of the small sample size (< 20 in each group), Hedges' *g* was also calculated for between study comparisons as effect size. *P* values < 0.05 were considered to be statistically significant.

3.7. Ethical Considerations

The approval code of the Ethics Committee of Shiraz University of Medical Sciences is 95-01-08-13957). Students signed written informed consent.

The control group was provided with the educational software content after the end of the study.

4. Results

The study results revealed that the students' mean ages were 22.78 ± 1.53 and 22 ± 1.34 years ($P = 0.17$), and the means of their average points were 15.87 ± 0.99 and 15.58 ± 1.65 ($P = 0.57$) in mobile learning and group discussion groups, respectively. Also, no significant differences were observed between the 2 groups with respect to sex distribution ($P = 0.74$). The rate of participation in research activities was 67% in the discussion group and 75% in

the mobile learning group ($P = 0.69$). The majority of students in both groups used the internet to find answers to their course questions, and no significant differences were observed between the 2 groups in this regard ($P = 0.40$). Overall, the 2 groups were similar with respect to all demographic characteristics (Tables 1 and 2).

Among the students receiving the educational intervention through the discussion group, the mean score of learning increased from 9.29 ± 2.09 in the pretest to 15.88 ± 1.65 in the posttest. In the mobile learning group, this measure increased from 9.85 ± 2.74 before the intervention to 14.74 ± 2.31 after the intervention. Thus, the educational interventions resulted in an increase in the rate of learning in both study groups. The results of the paired *t*-test also revealed a significant difference in the 2 groups' learning scores before and after the intervention ($P < 0.001$). However, no significant differences were detected between the 2 groups' learning scores at the 2 stages ($P = 0.15$; Hedges' *g* = 0.53; 95% CI, -0.20 to 1.27; Table 3).

The results of the paired *t*-test revealed a significant within-study difference in the discussion group's scores of satisfaction with the instruction method before and after the intervention (27.78 ± 5.07 vs 33.13 ± 5.51 ; $P = 0.02$). The results also indicated that the mobile learning group's score of satisfaction with the instruction method increased significantly after the intervention compared to the baseline intervention (31.56 ± 6.08 vs 38.69 ± 4.78 ; $P = 0.001$). Moreover, in the comparative analysis between the 2 study groups, the results of the independent *t*-test showed that the students in the mobile learning group were more satisfied with the instruction method compared with those in the discussion group ($P = 0.02$; Hedges' *g* = 1.09; 95% CI, 0.29-1.89; Table 4).

However, according to ANCOVA, no significant differences were found after adjustment for baseline satisfaction scores, age, and sex ($P = 0.09$). The results of the paired *t*-test also revealed a significant difference in the students' attitude scores before (46.38 ± 10.31) and after (52.13 ± 8.43) education using mobile phones ($P = 0.038$; Table 5).

5. Discussion

This study aimed to compare the effects of psychotropic drug education using group discussion and mobile learning on nursing students' learning, satisfaction, and attitude at Shiraz University of Medical Sciences. The results demonstrated an increase in the 2 groups' scores of learning and satisfaction with the instruction method after the intervention compared to baseline. Although the mobile learning group's

Table 1. Comparison of the 2 Groups Regarding Qualitative Demographic Features

Variables	Mobile Learning Group (n = 16; No. [%])	Group Discussion Group (n = 12; No. [%])	P-Value ^a
Sex			
Female	9 (56.2)	6 (50)	0.74 [*]
Male	7 (43.8)	6 (50)	
Participation in research activities			
Yes	12 (75.0)	8 (66.7)	0.69 ^{**}
No	4 (25.0)	4 (33.3)	
Membership in scientific websites			
Yes	5 (31.2)	5 (41.7)	0.57 [*]
No	11 (68.8)	7 (58.3)	
Finding the course questions			
Internet	12 (75)	8 (66.7)	0.69 ^{**}
Other	4 (25)	4 (33.3)	

^a Between-group comparisons were conducted using ^{*} chi-square or ^{**} Fisher's exact test. P values < 0.05 were considered significant.

Table 2. Comparison of the 2 Study Groups Regarding Quantitative Demographic Features ^{a, b}

Variables	Mobile Learning Group (n=16)	Group Discussion Group (n = 12)	P-Value
Age	22.78 ± 1.53	22 ± 1.34	0.17
Previous semesters' average point	15.87 ± 0.99	15.58 ± 1.65	0.57

^a Values are presented as Mean ± SD.

^b Between-group comparisons were conducted using independent samples *t*-tests. P values < 0.05 were considered significant.

Table 3. Comparison of the 2 Groups' Learning Scores Before and After the Intervention ^{a, b}

Learning Scores	Mobile Learning (n = 16)	Group Discussion Group (n = 12)	P-Value ^c
Before the intervention	9.85 ± 2.74	9.29 ± 2.09	0.59
After the intervention	14.74 ± 2.31	15.88 ± 1.65	0.15 ^d
Mean difference	4.94 ± 3.32	6.59 ± 2.81	0.17
P-value [*]	< 0.001	< 0.001	

^a Values are presented as Mean ± SD.

^b P values < 0.05 were considered significant.

^c Between group and ^{*} within group comparisons were conducted using the independent samples *t*-test and paired *t*-test, respectively.

^d Hedges' *g* = 0.53; 95% CI, -0.20 to 1.27.

Table 4. Comparison of the 2 Groups' Scores of Satisfaction with the Instruction Methods Before and After the Intervention ^{a, b}

Scores of Satisfaction	Mobile Learning (n = 16)	Group Discussion Group (n = 12)	P-Value ^c	P-Value ^d
Before the intervention	31.56 ± 6.08	27.78 ± 5.07	0.13	
After the intervention	38.69 ± 4.78	33.13 ± 5.51	0.02 ^e	0.09
Mean difference	8.15 ± 7.12	5.57 ± 4.96	0.41	
P-value [*]	0.001	0.02		

^a Values are presented as Mean ± SD.

^b P values < 0.05 were considered significant.

^c Between group and ^{*} within group comparisons were conducted using the independent samples *t*-test and paired *t*-test, respectively.

^d The P value related to the ANCOVA test after adjustment for the baseline value, age, and sex.

^e Hedges' *g* = 1.09; 95% CI, 0.29-1.89.

Table 5. Comparison of the Mobile Learning Group's Mean Scores of Attitudes Before and After the Intervention ^{a, b}

Scores of Attitudes	Mobile Learning (n = 16)
Before the intervention	46.38 ± 10.31
After the intervention	52.13 ± 8.43
Mean difference	5.75 ± 10.11
P-value ^c	0.038

^a Values are presented as Mean ± SD.

^b P values < 0.05 were considered significant.

^c The within-group comparison was conducted using a paired t-test.

satisfaction score was higher than that of the discussion group, the difference was not statistically significant after ANCOVA. The results also revealed a significant difference in the mobile learning group's score of attitudes after the intervention compared to before that. These results were consistent with those of numerous investigations, for instance, a study on using mobile phones for triage indicators among emergency nurses in 2018; the results demonstrated a significant increase in knowledge scores after the intervention compared to baseline (25). Another study investigated the impacts of using educational booklets and interactive multimedia using CDs on the prevention of osteoporosis among female students. The results revealed a significant increase in both groups' learning scores after the intervention compared to baseline (26). Similarly, 1 study compared the lecture method, electronic learning, and conceptual map on pediatric nursing education and came to the conclusion that all 3 methods were effective in the promotion of the students' knowledge and learning (13). Another compared the effects of anatomy instruction via mobile phone and lecture methods. The findings indicated an increase in both groups' learning scores after the training compared to baseline (27). In the present study, no significant differences were found between the 2 instruction methods with regard to changes in learning scores. These results are consistent with those of some other studies. Zarshenas et al reported no significant differences in learning scores between the interactive multimedia method and educational booklet (26). Another disclosed that cardiac patients' self-care training via computer and brochure caused an increase in knowledge scores in both study groups, but the difference between the 2 groups was not statistically significant (28). However, contradictory results were obtained in some other studies. For instance, comparing the effects of health education using mobile phone- and web-based discussion, it was reported that group discussion based on mobile phones provided more valuable opportunities for self-education, educational motivation, and interaction between the

learners and the learning process (29). Similarly, 1 study compared the effects of lecturing, problem-solving, and self-education through a computer on BSc nursing students' drug calculation skills in the intensive care course. The results indicated that all 3 methods were significantly correlated to the students' learning levels, but self-education through computer was less effective compared to the other 2 methods (30). Some studies showed that if the instructional design is standard, appropriate, and meticulous, there will be no significant differences in students' learning (31), but at the same time, lack of differences between the 2 groups' learning scores in the present study could be attributed to the advantages and disadvantage of the 2 instruction methods. The main strong points of education using mobile phones include lightness, small size, and portability of the educational device, accessibility to education at any time and place, flexible learning, application of multimedia techniques regardless of time and place, and provision of valuable learning opportunities at both dynamic and static times. On the other hand, the main disadvantages of this method include lack of face-to-face relationships, lack of concentration at the time of learning due to the attractiveness of mobile phones, lack of network coverage in some regions, learners' inability to organize the learning process, lack of technical and support infrastructures, lack of educational standards for changing traditional materials into the electronic format, and mobile phones' small LCDs and keyboards (32-35). Moreover, the main strong points of learning through group discussion include information exchange, ability to learn complicated materials, empowerment of reasoning, ability to evaluate viewpoints and make the best decisions, improvement of communication skills, and increasing learners' self-confidence. On the other hand, one of the limitations of this method is that a longer period of time is required for education because of the need for logical discussions among students, while a specific time is dedicated to educational plans in universities' curricula. Thus, students may not gain great benefits

from this method. Additionally, group discussion requires the instructor to manage the groups quite effectively. In case of instructor's inefficiency, this method may not be accompanied by high success rates. Moreover, this method is not appropriate for large groups and meetings (10). In the current study, the results of the paired *t*-test showed an increase in the 2 groups' scores of satisfaction with the instruction methods after the intervention compared to baseline. The results of the independent *t*-test also revealed that the satisfaction score with the instruction method was significantly higher in the mobile learning group compared to the discussion group. These results are consistent with some other studies (36-39). The software used in the current study benefitted from repeatability, visual and audio attractions, videos, animations, possibility to use the written format, and summary of the materials, which were effective in the students' high satisfaction levels. However, the results are in contrast to those of some other studies, including the one that evaluated the impact of education using mobile phones on nursing students' knowledge, skills, and self-confidence at the time of caregiving (40) or one which reported no significant differences between the intervention and control groups regarding the rate of satisfaction, which was attributed to the small sample size, as well as the students' inability to respond to E-mails due to large loads of homework (41). Similarly, 1 study compared the effects of traditional and novel instruction methods on dental students' knowledge and attitude and found no significant differences between the 2 groups with respect to satisfaction with the instruction method. Based on their perspective, this finding resulted from the novelty of the multimedia educational method (42). One research developed electronic learning for nurses. The results indicated no significant differences between the intervention and control groups, which was ascribed to the small sample size, as well as the loss of some participants due to limitations in the location of using computer facilities (43). All the above-mentioned studies showed no significant differences between the intervention and control groups. Students' interest in traditional lecture methods, internet and mobile phone limitations, and bandwidth limitations could also play a pivotal role in learners' dissatisfaction.

The results of the paired *t*-test revealed a significant increase in the mobile learning group's attitude scores after the intervention compared to the baseline. These results are consistent with those obtained in some other studies (22, 35, 44-47). However, contradictory results were obtained by other studies (41, 48). The controversy among the results could result from the advantages and disadvantages attributed to each of the educational

methods. The main advantages included interaction, accessibility, high motivation, cooperative learning, and flexibility. On the other hand, low transfer speed, bandwidth limitations, limited memory space, low internet speed for downloading images, videos, and animations, small LCD and keyboard, and relatively high cost were mentioned as the main disadvantages of mobile phones (35).

5.1. Limitations

One of the limitations of the present study is an obligation to use only 1 BSc nursing course during a short period of time. Another study limitation is its small sample size. Initially, we calculated the sample size for our trial based on certain assumptions and considerations. However, due to various practical constraints, such as difficulties in recruitment, we were unable to enroll the exact number of students as initially calculated. Despite enrolling a lower number of students than initially planned, we conducted a post hoc power analysis to assess the statistical power of our study (61%). Therefore, a larger sample size in future studies would have provided more robust results and increased precision. Low internet speed also caused a limitation in downloading educational videos.

5.2. Conclusions

The study results showed that psychotropic drug education through mobile learning and group discussion enhanced the students' learning of psychotropic drugs. However, a significant difference was observed between the 2 groups with respect to satisfaction with the instruction method. Indeed, the students developed a more positive attitude after the training compared to the baseline.

Considering the importance of students' learning of psychotropic drugs and its undeniable role in the promotion of nursing processes, patient care, and medication management, educational interventions are required for nursing students to improve their nursing care and medication management. In this context, university professors are recommended to make use of electronic methods for educational planning and developing educational curricula based on instructional design models. We recommend doing this study with the third group using the traditional methods of teaching and comparing it with group discussion and mobile learning.

Footnotes

Authors' Contribution: LZ, ZT, and MM designed and drafted the manuscript. LZ and ZT performed the statistical

analysis. AAK and EMS revised the manuscript and clinical data. All authors read and approved the final manuscript.

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