Clinical Pharmacist Role in Increasing the Adherence to Recommendations Among Patients Using Isotretinoin: a Randomized, Controlled Study

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Study Protocol

Study design and sites:

A randomized, controlled study will be conducted at the dermatology clinics in several Jordanian hospitals: King Abdullah University Hospital (KAUH), Princess Basma Hospital (PBH), King Talal Hospital (KTH), Princess Haya Hospital (PHH), Prince Rashid Hospital (PRH) and King Hussein Medical Center.

Patients

Patients who will come to the clinic to receive isotretinoin medication, with any brand names known in Jordan like (ISOSUPRA®, ROACCUTANE®,, CURANCE®,, RUATINE®,) and have the following criteria; male or female patients, ≥18 years who are diagnosed for the first time with moderate to severe acne vulgaris and receiving standard doses (0.5-1mg/kg/day), are willing to take the treatment, and to do follow-ups, will be approached and asked to participate in the study.

Patient with any contraindication to isotretinoin who cannot take the medication and patients who are not willing to participate in the study will be excluded. These contraindications are; age less than 12 years, patients having mild acne vulgaris, pregnant women and women who intend to become pregnant, breastfeeding women, presence of any renal or hepatic compromise, or any pre-existing hyperlipidemia.

A convenience sampling technique will be used to collect the study sample referring to a previous study [1]. Also using 30% effect size (difference in adherence between control (50%) and intervention group (80%)), alpha= 0.05, beta=0.8 and enrollment ratio=1 at least 45 patients should be enrolled in each group (results from OpenEpi, Version 3, open source calculator—SSCohort/ RCT) . To account for loss to follow-up, a minimum of 50 patients will be enrolled in each group.

After the informed consent (see appendix 1) is taken from each patient who agreed to participate in the study, the participants will be randomly assigned to either an intervention group or a control group. Intervention group will consist of the patients who will receive the educational process (recommendations) about isotretinoin by clinical pharmacists additionally to the usual routine care (education about isotretinoin provided by the physician). Control group will consist of the patients who will receive the usual routine care. Both patients and physicians are unaware of patients' assignment in both groups.

The main task of the clinical pharmacist is to educate patients in intervention group by providing them all information about isotretinoin that can serve the patient during the treatment period, which includes: the degree of the importance of adherence to the drug and the recommendations, the correct method of taking it, the importance, and when, of doing periodic laboratory tests (lipid profile, liver enzyme test, and pregnancy test), and explanation of common side effects, how to avoid and deal with them, and what are the cases in which the drug should be stopped. The detailed information on the recommendation for managing side effects that will be used to educate the patients are provided in Appendix 2.

Patient's adherence to the recommendations, awareness and side effects managements for both groups will be measured through a set of questions adapted from a validated questionnaire after one month and three months of isotretinoin initiation (Appendix 3). The validated questionnaire was was adopted from a previous study on patients' knowledge about isotretinoin therapy use in Jordan. The permission to use the questionnaire was obtained from the researcher.

The questionnaire is composed of 41 questions related to: demographics, side effects, physician and clinical pharmacist practice, recommendations and contraindications according to current guidelines, and patients' commitment. In addition, the Hospital Anxiety and Depression Scale (HADS) [22], will be used to evaluate depressive and anxiety symptoms at baseline and during the follow up period in each group. Finally, clinical improvement in acne will be evaluated three months after initiating the treatment from the view of physicians as well as the patients themselves.

Location and safety considerations

The dermatology clinics located in: King Abdullah University Hospital (KAUH), in Princess Basma Hospital, (PBH), King Talal Hospital (KTH), Princess Haya Hospital (PHH) and Prince Rashid Hospital (PRH) and King Hussein Medical Center will be visited for patients interview and data collection. The participants' privacy will be preserved throughout the study and the participants' answers will be kept strictly confidential and never associated with any personal details. This study does not involve any human biological sample. No potential risks will be associated with the participation in the current study. No special safety consideration for isotretinoin drug Except those mentioned above since it approved from 1982. Consent will be obtained from IRB.

Data analysis

After data was collected, the data was entered into Excel worksheets. The responses were coded and entered into SPSS (version 23). Descriptive statistics of categorical and continuous variables were

calculated. For the categorical variables, the frequency and percentage were calculated, while the arithmetic mean and standard deviation were calculated for continuous variables.

The differences in participants' responses were examined using the Chi-square test (between intervention and control groups) and McNamara's test (between baseline and follow up encounters) for categorical dependent variables as appropriate. For continuous dependent variables, One Way Analysis of Variance (ANOVA) test, independent samples t-test, and Wilcoxon test were performed when applicable. Both Kolmogorov-Smirnov Z and Shapiro-Wilk tests were used to test for normality of continuous variables. The statistical significance level was considered at a p-value ≤ 0.05.

Patients Knowledge and Awareness of Isotretinoin:

The degree of knowledge and awareness of correct practice was calculated as a total score. The patient knowledge section consisted of ten different questions/items, and each item had two answers (yes/no). Items were coded according to the answer; the correct (adequate) answer was coded as one (1), while the wrong (not adequate) answer was coded as zero (0). So, the knowledge score could take the values of 0 (no knowledge) to 10 (perfect knowledge).

Chi square test was used to measure patients' knowledge regarding isotretinoin use at baseline between intervention and control group. It was also used to measure patients' knowledge regarding isotretinoin use at follow-up between intervention and control group. To measure if there was a significant difference in the correct patient knowledge regarding isotretinoin use, the percentage of the correct response for each question was calculated for both groups in baseline and at follow-up. McNamara's test was performed to test if there was a significant difference in knowledge before the intervention and after the intervention in the intervention group, and at if there was a significant difference in knowledge between baseline and follow-up in the control group. In addition, independent t-test was used to compare the knowledge score differences (knowledge score at follow up – knowledge score at baseline) between the intervention group and the control group. Linear regression was conducted to evaluate the effect of the educational intervention on the difference in knowledge score adjusting to variables that were unbalanced at baseline.

Patients Adherence to the Recommendations

Similarly, adherence to recommendations for appropriate uses provided by clinical pharmacists for correct practice was calculated as a total score for each participant. This section consisted of 10 items for all patients, and each item had answers (yes/no). Items were coded according to the answer; the correct (adherent) answer was coded as one (1), while the wrong (not adherent) answer was coded as

zero (0). The adherence score of patients 'compliance with the recommendations ranged between 0 (least adherent) to 10 (most adherent). Average score was evaluated across the intervention and control groups (using t test).

HADS Scale

HADS questionnaire was analyzed based on the scoring system; which consists of fourteen items; seven items each for the depression and anxiety subscale. The score for each item ranges from 0 to 3, and the HADS score ranged from 0 to 21 for depression and the same applied for anxiety.

Chi square test was used to compare HADS items at baseline between intervention and control group. Besides, it was used to compare HADS items at follow-up between intervention and control group. Independent t-test was used to compare the HADS score differences (between baseline and at follow up) between the intervention group and the control group.

HADS scores were categorized into three categories based on the abnormality classification; normal (less than eight), borderline abnormal (between eight and eleven) and abnormal (above eleven). Chi square test was used to evaluate the association between HADS score categories and intervention control status at baseline and at follow up.

Patients Adherence to Medication

The percentages (%) of patients' adherence to medication and non-pharmacological adherence were calculated by dividing the number of adherent patients by the total number of patients in both groups. According to the final question, the reasons behind the patient's non-adherence were themed into three distinct groups (forgetfulness, run out, and unavailability of isotretinoin). The frequency (%) of each group was calculated by dividing the number of times each category has occurred over the total number of patients and multiplying by 100.Chi-square test was conducted to evaluate the association between adherence status and patient intervention control status.

Results

1. Baseline Questionnaire Results

A total of 207 patients using isotretinoin in Jordan were randomly recruited to participate in the study. About four patients missed answering the phone in the follow-up phase, so they were excluded from the study. The response rate was 96.7% and 203 patients completed the study as shown in **Figure 1**.

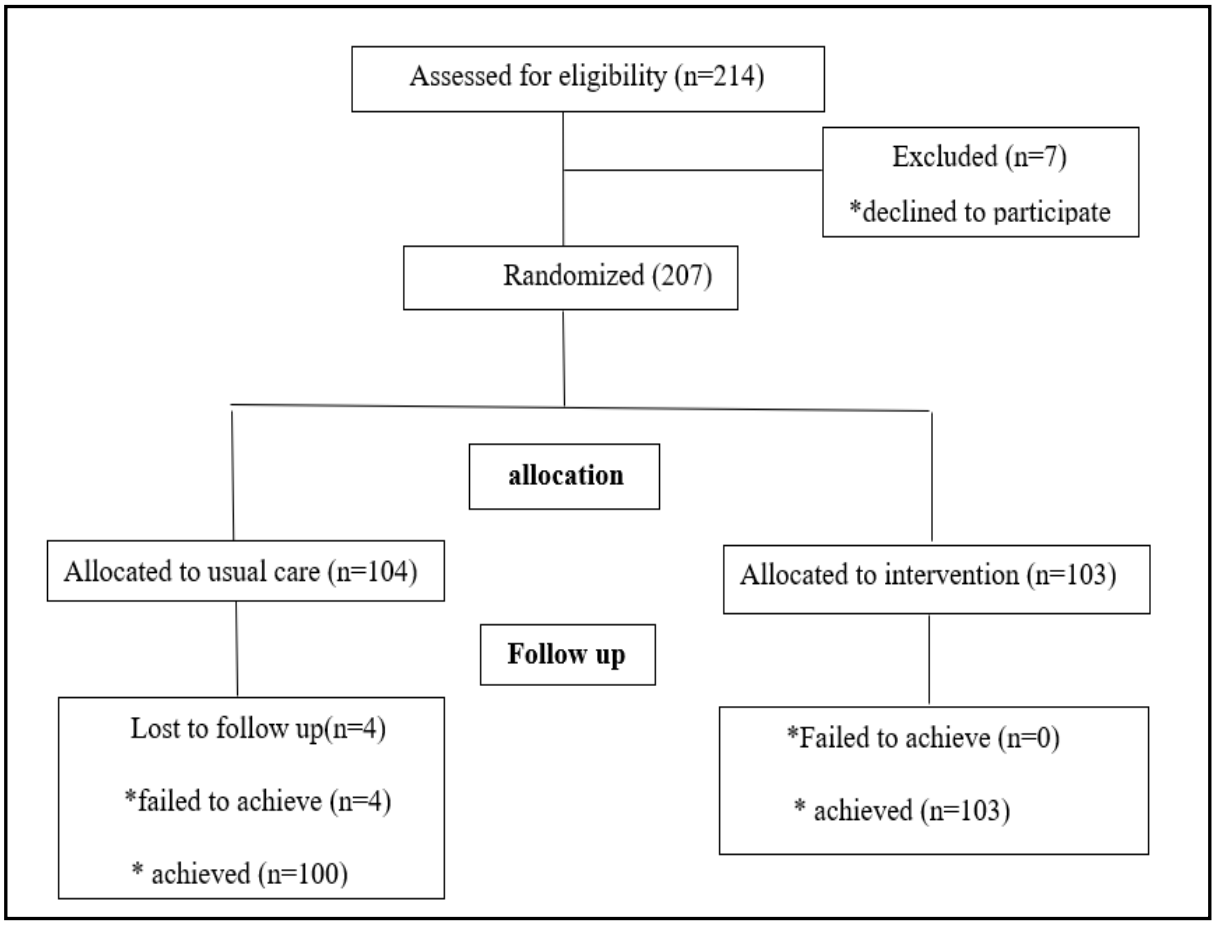

Figure 1: Patient recruitment flowchart

1. Demographics of Respondents

The demographics of the participants are summarized in **Table 1**. All baseline demographic and clinical characteristics of the study participants were not statistically different between intervention and control group except for monthly income with P-value=0.032. Most respondents were female (n=179, 88.2%) compared to male (n=24, 11.8%) in both groups. Most of the patients were in the age group of 18-25 years, and the mean ± SD of age for the intervention group was 21.68 ± 3.21 and 21.36 ± 2.6 for the control group. Regarding marital status, 96.9% of the participants were single

while the remaining were married (3.1%) for both study groups. The vast majority of participants have a bachelor's degree in both the intervention (85%) and control groups (86%). Most of the respondents' area of the residence for both groups was from the Irbid (77.8%) and the rest were from other cities (22.2%). Patients in either intervention or control group had a body mass index (BMI) ranged between 18.5 and 24.9 with a percentage of 68.6% and 73%; respectively.

Regarding health insurance, 96.1% of the intervention group and 98% of the control group were insured. For all study participants, the period since starting to use the drug was no more than the first four months. More than half of the participants took a daily dose of 40 mg of isotretinoin in both intervention (58.3%) and control group (57%). The vast majority of the patients in both study groups (99%) had no chronic disease.

Table 4.1: Baseline demographic and clinical characteristics of the study population

Characteristics	Total		Intervention group		Control group		P-value
	n	%	n	%	n	%	
Gender							
female	179	88.20	91	88.30	88	88	
male	24	11.80	12	11.70	12	12	0.939
Age (years)							
18-20	86	42.40	41	39.80	45	45	
21-25	100	49.20	51	49.50	49	49	
26-30	13	6.40	7	6.80	6	6	
31-35	4	1.90	4	3.90	0	0	0.628
Marital status							
single	196	96.90	98	95.10	98	98	
married	7	3.10	5	4.90	2	2	0.265
Educational level							
school	21	10.30	10	9.70	11	11	
college	4	2	2	1.90	2	2	
bachelor	173	85.20	87	85	86	86	
postgraduate studies	5	2.50	4	3.90	1	1	0.562
Profession							
student	146	71.9	74	71.80	72	72	
Unemployed	25	12.3	10	9.70	15	15	
Non-medical profession	16	7.9	10	9.70	6	6	
Medical profession	16	7.9	9	8.70	7	7	0.525
Residential area							
Irbid	158	77.80	80	77.70	78	78	
Alzarqa'a	3	1.50	2	1.90	1	1	
AL Mafraq	13	6.40	7	6.80	6	6	
Amman	19	9.40	9	8.70	10	10	0.949

Jerash	4	2	2	1.90	2	2	
Ajloun	5	2.50	2	1.90	3	3	
Maan	1	0.50	1	1	0	0	
Monthly income							
below 500 JD	28	13.80	17	16.50	11	11	
500-100 JD	111	54.70	47	45.60	64	64	
above100 JD	64	31.50	39	37.90	25	25	0.032
Health insurance							
yes	197	97	99	96.10	98	98	
No	6	3	4	3.90	2	2	0.428
Strength & dose of isotretinoin per a day (mg)							
10	2	1	2	1.90	0	0	
20	55	27.10	26	25.20	29	29	
30	26	12.80	14	13.65	12	12	
40	117	57.60	60	58.30	57	57	
60	3	1.50	1	1	2	2	0.612
Period since starting the current isotretinoin course (months):							
newly diagnosed	42	20.70	22	21.40	20	20	
first month	42	20.70	23	22.30	19	19	
second month	51	25.10	26	25.20	25	25	
third month	57	28.1	29	28.20	28	28	
fourth month	11	5.40	3	2.90	8	8	0.603
Body mass index							
under 18.5	23	11.40	11	10.80	12	12	
18.5-24.9	143	70.40	70	68.60	73	73	
25-29.9	28	13.90	15	14.70	13	13	
30-34.9	7	3.50	5	4.90	2	2	
35-39.9	2	1	1	1	1	1	0.783
Total	203	100	103	50.7	100	49.3	

2. General Information Regarding Isotretinoin Use

All patients (100%) were taking isotretinoin based on an authorized prescription. On the other hand, 10.8% of sampled patients had been taking isotretinoin at least once without a prescription prior to current use; 10.7% of intervention group and 11%of control group with P-value = 0.941. While 89.2% had never used isotretinoin before without prescription; 89.3% of the intervention group and 89% of the control group. 59.2% of the intervention group and 67% of the control group did not visit a dermatologist for acne problems for the first time but did so several times before starting isotretinoin with a P-value=0.251.

Participants were asked to answer two questions regarding laboratory testing (liver function test and lipid profile test), whether these tests were required to be performed, and if they did check them before starting treatment. Results showed that 98.1% of intervention group and 98% of control group

were required to undergo testing with P-value=0.976, while 97.1% of the intervention group and 97% of the control group with P-value=0.971 were checked these tests. Approximately 69.5% of enrolled patients said that their physicians informed them about the expected side effects of isotretinoin and how to manage it; 72.8% of the intervention group and 66% of the control group with P-value=0.327.

During the questionnaire, participants were asked to answer two questions about the impact of having acne on their daily, psychological and social life, about the severity of their acne condition, and results are summarized in Figure 2 and Figure 3; respectively.

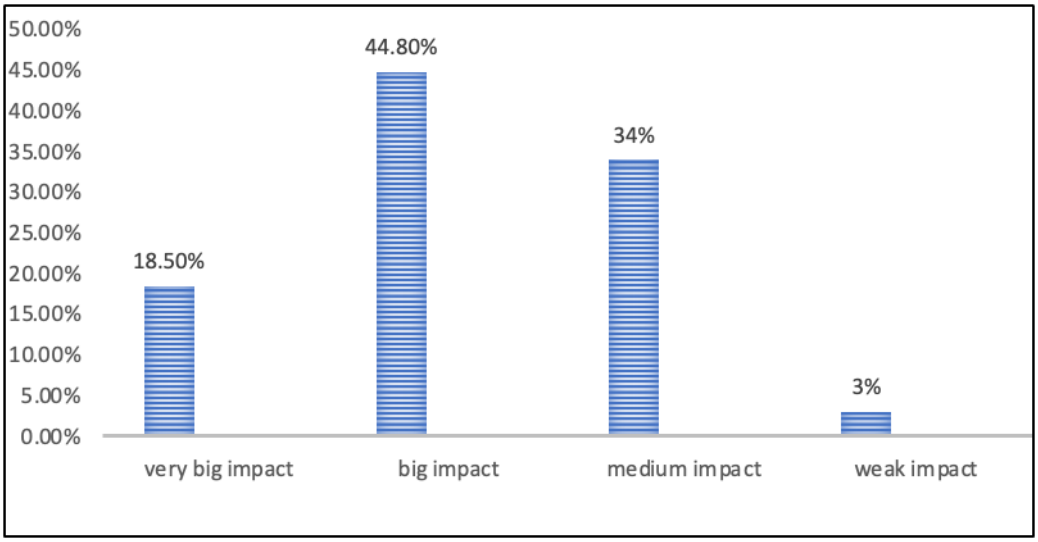

Figure 2: The impact of acne on daily, psychological, and social life.

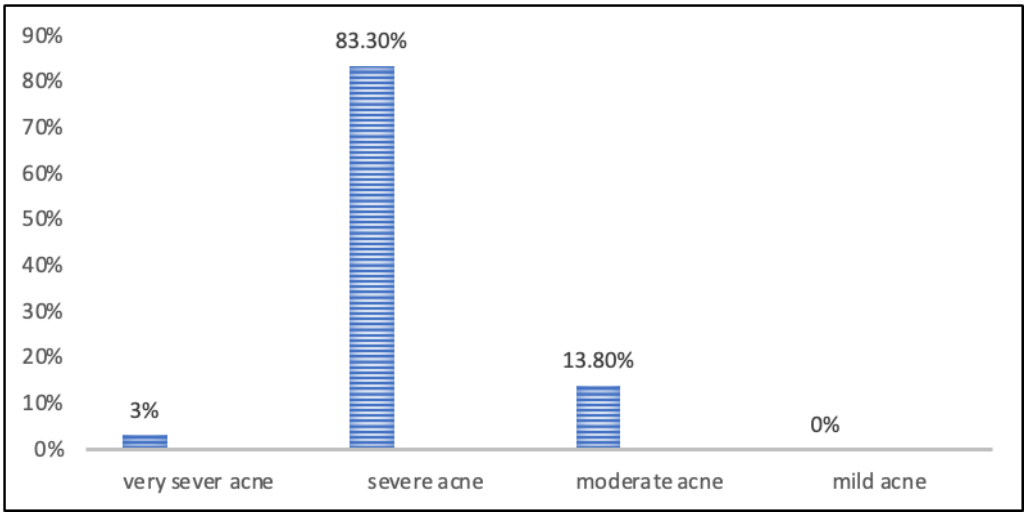

Figure 3: The severity of acne condition as reported by participants.

3. Patients Knowledge about Isotretinoin Use

Patients' knowledge about isotretinoin treatment for both groups was assessed at baseline and at the

3 months follow-up, and responses of the patients are shown in **Table 2** and **Table 3**; respectively. Patients' average knowledge score at the first meeting before the education process was 6.5 out of 10. There was no significant difference in overall knowledge score at baseline between the intervention group and the control group with a mean (6.47 for the intervention group vs. 6.57 for the control group).. In contrast, the patient's average knowledge score at follow-up (three months after the education session) was 8.22 out of 10. The results at follow-up showed a significant difference in the knowledge score (P-value<0.001) between the intervention (9.3) and control group (7.1).

The average difference in the overall knowledge score (before and after the education process) was statistically different between the intervention and control group (1.6995±1.589; P-value< 0.001). The average difference in overall knowledge score was, 2.835±1.329 for the intervention group and 0.530±0.784 for the control group.

Since the monthly income was significantly different between intervention group and control group at baseline, results from linear regression showed that the difference in overall knowledge score is still significantly different between the intervention and control group after adjustment for income status (Coef. = 2.308446); P-value< 0.001

Table 2: Patients knowledge regarding the use of isotretinoin at baseline

	Intervention group n (%)	**Control group n (%)**	**P-value**
knowledge about common side effects			
yes	6 (5.8)	2 (2)	
no	97 (94.2)	98 (98)	0.28
We can use isotretinoin during pregnancy*			
yes	10 (9.7)	10 (10)	
no	93 (90.3)	90 (90)	0.944
We can use the drug without prescription*			
yes	6 (5.8)	5 (5)	
no	97 (94.2)	95 (95)	0.795
No need to have laboratory monitoring during isotretinoin use*			
yes	4 (3.9)	5 (5)	
no	99 (96.1)	95 (95)	0.745
We should drink water to reduce the dryness			
yes	99 (96.1)	98 (98	
no	4 (3.9)	2 (2)	0.683
We should use sunblock to reduce sensitivity to the sun			
yes	99 (96.1)	99 (99)	
no	4 (3.9)	1 (1)	0.121
It is preferred to take isotretinoin with fatty foods			
yes	70 (68)	74 (74)	0.343

no	33 (32)	26 (26)	
We can donate blood during isotretinoin*			
yes	67 (65)	70 (70)	
no	36 (35)	30 (30)	0.451
Woman can lactate while using isotretinoin*			
yes	72 (69.9)	72 (72)	
no	31 (30.1)	28 (28)	0.742
We can make laser or wax during isotretinoin*			
yes	66 (64.1)	55 (55)	
no	37 (35.9)	45 (45)	0.188

The correct answer is yes unless otherwise indicated. * The correct answer is no.

Table 3: Patients knowledge regarding the use Isotretinoin at follow-up

	Intervention group-post n (%)	**Control group-post n (%)**	**P value**
knowledge about common isotretinoin side effects			
yes	49 (47.6)	3 (3)	
no	54 (52.85)	97 (97)	< 0.001
We can use isotretinoin during pregnancy*			
yes	0 (0)	4 (4)	
no	103 (100)	96 (96)	0.057
We can use the drug without prescription*			
yes	0 (0)	5 (5)	
no	103 (100)	95 (95)	0.028
No need to have laboratory monitoring during isotretinoin use*			
yes	0 (0)	5 (5)	
no	103 (100)	95 (95)	0.028
We should drink water to reduce the dryness			
yes	100 (97.1)	98 (98)	
no	3 (2.9)	2 (2)	0.675
we should use sunblock to reduce sensitivity to the sun			
yes	103 (100)	99 (99)	
no	0 (0)	1 (1)	0.493
It is preferred to take isotretinoin with fatty foods			
yes	103 (100)	81 (81)	
no	0 (0)	19 (19)	< 0.001
We can donate blood during isotretinoin*			
yes	0 (0)	57 (57)	
no	103 (100)	43 (43)	< 0.001
Woman can lactate while using isotretinoin*			
yes	9 (8.7)	60 (60)	
no	94 (91.3)	40 (40)	< 0.001
We can make laser or wax during isotretinoin*			

yes	5 (4.9)	40 (40)	
no	98 (95.1)	60 (60)	< 0.001

The correct answer is yes unless otherwise indicated. * The correct answer is no.

The percent of correct answers were significantly higher at follow up compared to baseline for most of knowledge questions in the intervention group. On the other hand, the percent of correct answers were significantly higher at follow up compared to baseline for the five out of the ten knowledge questions in the control group as shown in **Table 4.**

Table 4: Patient knowledge regarding isotretinoin use at baseline and at follow up.

	Intervention group- baseline n (%)	**Intervention group- follow up n (%)**	**P -value**	**Control group- baseline n (%)**	**Control group- follow up n (%)**	**P-value**
knowledge about common isotretinoin side effects						
	6 (5.8)	49 (47.6)	< 0.001	2 (2)	3 (3)	0.564
We can use isotretinoin during pregnancy*						
	93 (90.3)	103 (100)	0.0016	90 (90)	96 (96)	0.0339
We can use the drug without prescription*						
	97 (94.2)	103 (100)	0.0143	95 (95)	95 (95)	0.95
No need to have laboratory monitoring during isotretinoin use*						
	99 (96.1)	103 (100)	0.0455	95 (95)	95 (95)	0.95
We should drink water to reduce the dryness						
	99 (96.1)	100 (97.1)	0.705	98 (98)	98 (98)	0.98
we should use sunblock to reduce sensitivity to the sun						
	99 (96.1)	103 (100)	0.045	99 (99)	99 (99)	0.317
It is preferred to take isotretinoin with fatty foods						
	70 (68)	103 (100	< 0.001	74 (74)	81 (81)	0.0196
We can donate blood during isotretinoin*						
	36 (35)	103 (100)	< 0.001	30 (30)	43 (43)	0.0008
Woman can lactate while using isotretinoin*						
	31 (30.1)	94 (91.3)	< 0.001	28 (28)	40 (40	0.0027
we can make laser or wax during isotretinoin*						
	37 (35.9)	98 (95.1)	<0.001	45 (45)	60 (60)	0.0011

Frequencies and percentages presented are for correct answers.

At follow-up, patients were asked if they searched for outside sources for information about the drug during their treatment. About 56% of the control group compared to 45% of the intervention group said yes with P-value=0.079.

4. Patient's Adherence to Recommendations About the Proper Use

The patient's adherence to recommendations for the proper use of isotretinoin and the adherence to

specific instructions on managing side effects provided by the physician or clinical pharmacist at follow-up was evaluated. The average recommendation score was 7.601 ±1.358 for all patients, and it was significantly different between control and intervention group (the mean for intervention group=8.534±0.905 and control group=6.64±1.039) with P-value <0.001. The percentage of participants who were adherent to all recommendations (10 out of 10) was 15.5% for the intervention group compared to 0% for the control group.

The frequency and number for patients who were adherent to the recommendations for the intervention group and control group are summarized in **Table 4.5**. Around 59% of the intervention group compared to 27% of the control group were adherent to drinking plenty of water (more than two liters per day) with P-value<0.001.

Table 5: Patient's adherence to recommendations about the proper use at follow-up

	Intervention group n (%)	**Control group n (%)**	**P value**
I adhere to drink plenty of water during isotretinoin use			
yes	61 (59.2)	27 (27)	< 0.001
no	42 (40.8)	73 (73)	
I adhere to use eye drop during isotretinoin use			
yes	89 (86.4)	69 (69)	0.003
no	14 (13.6)	31 (31)	
I adhere to use lip balm during isotretinoin use			
yes	101 (98.1)	98 (98)	0.90
no	2 (1.9)	2 (2)	
I adhere to use body lotion during isotretinoin use			
yes	48 (46.6)	28 (28)	0.006
no	55 (53.4)	72 (72)	
I adhere to make laboratory monitoring (AST & ALT) during isotretinoin use			
yes	102 (99)	98 (98)	0.618
no	1 (1)	2 (2)	
I adhere to make lipid profile test during isotretinoin use			
yes	102 (99)	98 (98)	0.618
no	1 (1)	2 (2)	
I adhere to use sunblock when going out during isotretinoin use			
yes	98 (95.1)	91 (91)	0.244
no	5 (4.9)	9 (9)	
I adhere to take isotretinoin with fatty foods			
yes	88 (85.4)	62 (62)	< 0.001
no	15 (14.6)	38 (38)	
I adhere not to donate blood during isotretinoin use			
yes	103 (100)	43 (43)	< 0.001
no	0 (0)	57 (57)	
I adhere not to make laser or wax during isotretinoin use			

yes	87 (84.3)	51 (51)	< 0.001
no	16 (15.7)	49 (49)	

Results showed that 86.4% of the intervention group compared to 69% of control group were adherent to the use of eye drop, and the difference was statistically significant (P-value=0.003). The adherence to using body lotion was higher in the intervention group (46.6%) compared to the control group (28%) with a P-value=0.006. On the other hands, there were no significant differences between both groups regarding the use of lip balm and sunblock.

For the two questions about adherence to laboratory monitoring (i.e., the liver function test or the lipid profile test), the rate of adherence was high in both group (99% for the intervention group and 98% for the control group) with no significant statistical difference.

The results of responses to the last three questions about adherence (taking the medication with or after fatty meals, adherence to not donate blood, and not to make laser or wax during treatment) were significantly different between the control and intervention group with P-value <0.001.

5. HADS Scale

HADS-Anxiety score and HADS-Depression score were tested at baseline and at follow-up after three months. At baseline, the mean HADS-Anxiety score for both groups was 7.8079±4.159, which slightly improved to 7.5862±3.28 at follow-up, which was statistically not significant. Likewise, the mean HADS-Depression score was 6.773±3.709, while at follow-up it became 7.0148±3.1029 and it was statistically not significant. The responses for intervention and control group at follow-up (intervention vs. control group) are indicated in **Table 6**.

Table 6: HADS anxiety and depression score at follow-up

	Intervention group n (%)	**Control group n (%)**	**P-value**
I feel tense or 'wound up.'			
most of the time	4 (3.9)	2 (2)	
a lot of the time	20 (19.4)	7 (7)	
from time to time	54 (52.4)	75 (75)	
not all time	25 (24.4)	16 (16)	0.006
I get a sort of frightened feeling like 'butterflies' in the stomach:			
very often	3 (2.9)	1 (1)	
Quite Often	26 (25.2)	15 (15)	
Occasionally	56 (54.4)	59 (59)	
not at all	18 (17.5)	25 (25)	0.163
I get a sort of frightened feeling as if something awful is about to happen			
very definitely and quit badly	10 (9.7)	5 (5)	
yes, but not too badly	30 (29.1)	27 (27)	
a little, but it does not worry me	55 (53.4)	59 (59)	0.577

not at all	8(7.8)	9 (9)	
I feel restless as I have to be on the move:			
Very much indeed	2 (1.9)	0 (0)	
Quite a lot	21 (20.4)	18 (18)	
not very much	57 (55.3)	64 (64)	
not at all	23 (22.3)	18 (18)	0.362
Worrying thoughts go through my mind:			
A great deal of the time	9 (8.7)	4 (4)	
A lot of the time	38 (36.9)	35(35)	
From time to time, but not too often	54 (52.4)	57 (57)	
not occasionally	2 (1.9)	4(4)	0.432
I get sudden feelings of panic			
Very often indeed	2 (1.9)	0 (0)	
Quite often	6(5.8)	4 (4)	
Not very often	35 (34)	34 (34)	
not at all	60(58.3)	62 (62)	0.493
I can sit at ease and feel relaxed:			
Definitely	12 (11.7)	11 (11)	
usually	47 (45.6)	54(54)	
Not Often	43 (41.7)	34 (34)	
not at all	1 (1)	1(1)	0.674
I feel as if I am slowed down			
Nearly all the time	1 (1)	1 (1)	
very often	19 (18.4)	15 (15)	
sometimes	73 (70.9)	76 (76)	
not at all	10 (9.7)	8 (8)	0.871
I still enjoy the things I used to enjoy:			
definitely as much	17 (16.5)	12 (12)	
not quite so much	43 (41.7)	54 (54)	
only a little	36 (35)	30 (30)	
hardly at all	7 (6.8)	4 (4)	0.33
I have lost interest in my appearance			
Definitely	0 (0)	1 (1)	
I do not take as much care as I should	2 (1.9)	0 (0)	
I may not take quite as much care	16 (15.5)	11 (11)	
I take just as much care as ever	85 (82.5)	88 (88)	0.269
I can laugh and see the funny side of things:			
As much as I can always could	31 (30.1)	31 (31)	
Not quite so much now	42 (40.8)	49 (49)	
Definitely not so much now	29 (28.2)	19 (19)	
not at all	1 (1)	1 (1)	0.461
I look forward with enjoyment to things:			

As much as I ever did	36 (35)	27 (27)	
Rather less than I used to	35 (34)	56 (56)	
Definitely less than I used to	31 (30.1)	16 (16)	
Hardly at all	1 (1)	1 (1)	0.012
I feel cheerful:			
Most of the time	12 (11.7)	10 (10)	
Sometimes	49 (47.6)	57 (57)	
Not often	41 (39.8)	33 (33)	
Not at all	1 (1)	0 (0)	0.456
I can enjoy a good book or radio or TV program:			
Often	21 (20.4)	15 (15)	
Sometimes	45 (43.7)	47 (47)	
Not often	25 (24.3)	28 (28)	
Very seldom	12 (11.7)	10 (10)	0.717

The average difference in anxiety score (difference between baseline and follow up) was not significant between intervention and control group (P-value=0.238) Similarly, the average difference in depression score was not significant between intervention and control group (P-value=0.323).

HADS score categories for both anxiety and depression subscales were not associated with the intervention control status at baseline nor at follow up. **Table 7** summarizes the results for follow-up.

Table 7: Comparison between intervention and control groups in HADS percentages at baseline and follow-up

	HADS-baseline (%)		**P-value**	**HADS-follow up (%)**		**P-value**
	Intervention	**Control**		**Intervention**	**Control**	
Anxiety score						
less than 8	45.60	55	0.283	49.50	55	0.536
8 _11	24.30	24		26.20	27	
above 11	30.10	21		24.30	18	
Depression score						
less than 8	55.30	64	0.108	58.30	64	0.288
8 _11	21.40	24		20.40	23	
above 11	23.30	12		21.40	13	

6. Patient Adherence

7. Pharmacological Adherence

The descriptive results of drug-taking behavior and the adherence at follow-up for all patients are presented in **Table 8**.

Table 8: Descriptive statistics of patient's answer to adherence questionnaire

	Intervention group	**Control group**

	n (%)	n (%)
Do you forget taking your medication		
Never	42 (40.8)	31 (31)
Rarely	51 (49.5)	51 (51)
sometimes	10 (9.7)	18 (18)
Usually	0 (0)	0 (0)
Always	0 (0)	0 (0)
Do you stop your medication when you feel better		
Never	103 (100)	98 (98)
Rarely	0 (0)	2 (2)
sometimes	0 (0)	0 (0)
Usually	0 (0)	0 (0)
Always	0 (0)	0 (0
Do you stop your medication when you feel worse		
Never	103 (100)	98 (98)
Rarely	0 (0)	2 (2)
sometimes	0 (0)	0 (0)
Usually	0 (0)	0 (0)
Always	0 (0	0 (0)
Do you run out of your medication		
Never	67 (65)	43 (43)
Rarely	31 (30.1)	48 (48)
sometimes	5 (4.9)	9 (9)
Usually	0 (0)	0(0)
Always	0 (0)	0 (0)
Do you adhere to lifestyle recommendations		
Never	0 (0)	1 (1)
Rarely	1 (1)	0 (0)
sometimes	2 (1.9)	1 (1)
Usually	51 (45.5)	78 (78)
Always	49 (47.6)	20 (20)

Out of the 203 patients in the study, 17.7 % reported that they were non-adherent to isotretinoin medication at follow-up (adherence score <4). Patients were grouped into adherent, non-adherent as previously indicated in the methodology chapter. Overall, 12.65% of the patients in the intervention were non-adherent vs. 23% in the control group (P-value=0.053). Regarding adherence items, 9.7% of intervention group and 18% of the control group said they sometimes, usually or always forget taking their medications (non-adherent); with a P-value =0.087. None of the patients in the intervention and control group said that they tended to stop taking their medications when they feel better or worse. 4.9% of the intervention group and 9% of the control group ran-out of their medications before they had the chance to refill them; P- value=0.244. Adherence to lifestyle recommendations was reported by 97.5% for all patients in both groups. The difference in non-

pharmacological level of adherence was not statistically significant between both groups; 98% of the control group were adherent and 97.1 % of the intervention group were adherent, as shown in **Table 9**.

Table 9: Comparison the prevalence of adherence between intervention and control group

	Intervention group (%)	Control group (%)	P-value
Do you forget taking your medication			
adherent	90.30	82	0.087
non-adherent	9.70	18	
Do you stop your medication when you feel better			
adherent	100	100	0.99
Non-adherent	0	0	
Do you stop your medication when you feel worse			
adherent	100	100	0.99
non-adherent	0	0	
Do you run out of your medication			
adherent	95.10	91	0.244
non-adherent	4.90	9	
total pharmacological score			
adherent	87.40	77	0.053
non-adherent	12.65	23	
Do you adhere to lifestyle recommendations			
adherence	97.10	98	0.675
non-adherent	2.90	2	

The causes of patients' non-adherence to medications are presented in **Figure 4.4**. Among 203 patients, the cause for patients not being adherent to their medications was forgetfulness (69%), followed by run out of isotretinoin (20%), unavailability of medication (4.5%), and lack of motivation (1%).

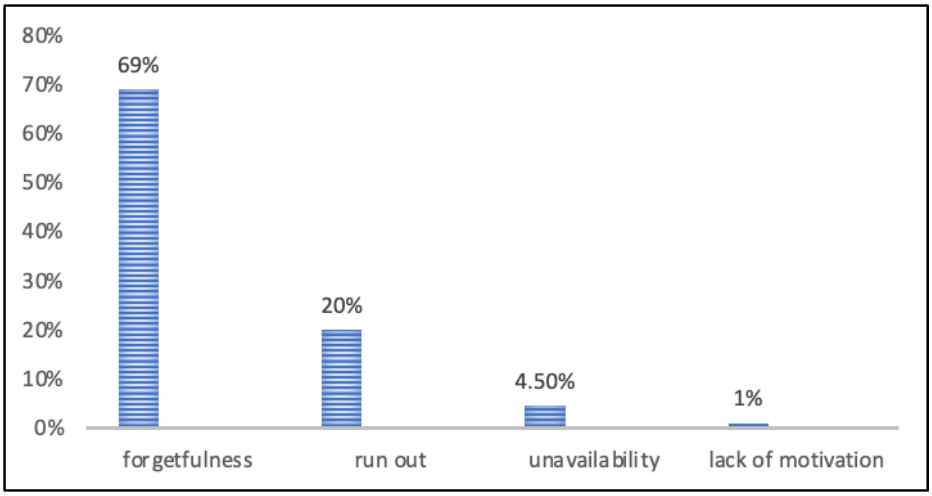

Figure 4: Causes of patients' non-adherence to medications

8. Miscellaneous

In the follow-up questionnaire, multiple additional questions were asked regarding patients' opinion about acne improvement, the impact of side effects on their daily activities, and their satisfaction with the provided drug information. There were statistically significant differences in all these three dimensions between the intervention and control groups.

About 47% of the patients who received the educational process from the clinical pharmacist in addition to the doctor reported that they had an excellent improvement in their acne conditions compared to 30% of the patients who received the educational process from the doctor only, P-value =0.048. Results are shown in **Table 10.**

Table 10: Patient's opinions about the improvement of the acne

	Intervention group n (%)	**Control group n (%)**	**P value**
In your opinion, how much is the improvement of your acne			
Excellent	48 (46.6)	30 (30)	
very good	50 (48.5)	56 (56)	
good	5 (4.9)	5 (5)	0.048

There was a significant difference between the intervention group and the control group with regards to the impact of side effects on daily life and normal activities of the patients, P-value<0.001. 76.6% of patients in the intervention group reported no effect or a weak effect on daily activity compared to 48% of the patients in the control group as indicated in **Table 11.**

Table 11: Patient's responses about side effect and their impact on daily activity

	Intervention group n (%)	**Control group n (%)**	**P-value**
How does the side effects affect your daily life and your normal activities			
Big impact	0 (0)	4 (4)	
Moderate impact	24 (23.3)	48 (48)	
Weak impact	73 (70.9)	46 (46)	
There is no impact	6 (5.8)	2 (2)	< 0.001

There are three questions about the patient's satisfaction with the provided drug information (either through the usual care provided by the doctor or the additional care provided by the clinical pharmacist in addition to the doctor). There were significant differences between the two groups with more satisfaction for the intervention group; 0% of the intervention group compared to 52% of the control group said they need more explanation about the drug with P-value<0.001. In addition, none of the intervention group compared to 71% of the control group said they need more

explanation about the side effects and how to avoid them with P-value<0.001. 17.5% of the intervention group compared to 44% of control group reported that they need more follow-up by the doctor with P-value<0.001. All the results of responses are presented in **Table 12.**

Table 12: Patient's satisfaction with the drug information

	Intervention group n (%)	**Control group n (%)**	**P-value**
Do you think you needed to explain more about the drug in general			
yes	0 (0)	52 (52)	< 0.001
no	103 (100)	48 (48)	
Do you think you need more explanations about the side effects and how to avoid it			
yes	0 (0)	71 (71)	< 0.001
no	103 (100)	29 (29)	
Do you think you need more follow-up by the doctor			
yes	18 (17.5)	44 (44)	< 0.001
no	85 (82.5)	56 (56)	

There was an additional question regarding the effect of COVID-19 pandemic on their treatment (as the study was conducted during the pandemic), the answer was around 90% of all patients' treatment were not affected, and only 10% affected (either little, medium, or big impact), the distribution of responses is presented in **Figure 5**.

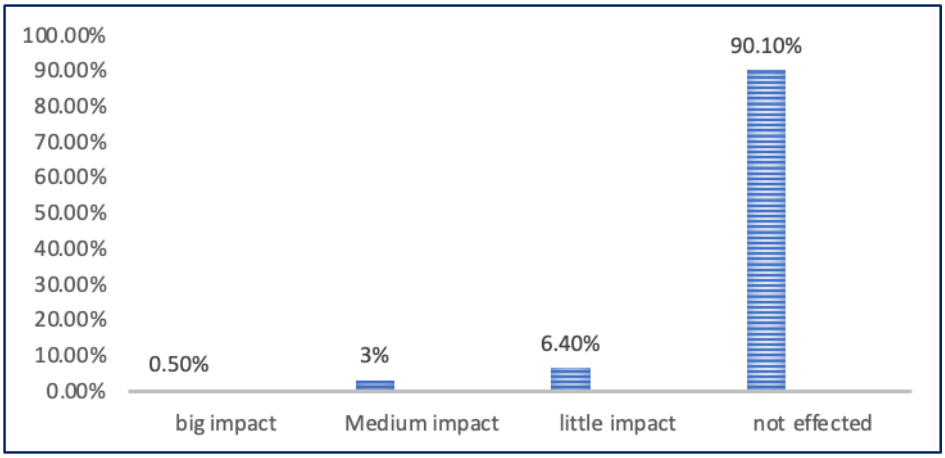

Figure 5: The effect of COVID-19 pandemic on the isotretinoin treatment.

Furthermore, the analysis of how the treatment was affected during the Corona period was checked for the patients and presented in **Figure 6**. The analysis showed that most of the patients reported an effect on their isotretinoin treatments. 70% of the patients were affected by their treatment due to the inability to go to monthly visits, and 45% of the patients were affected by the inability to obtain the medicine, and 1% of the patients were affected by the inability to make laboratory monitoring test, and 1% were affected by the inability to adhere to isotretinoin when they were infected with COVID-19 virus.

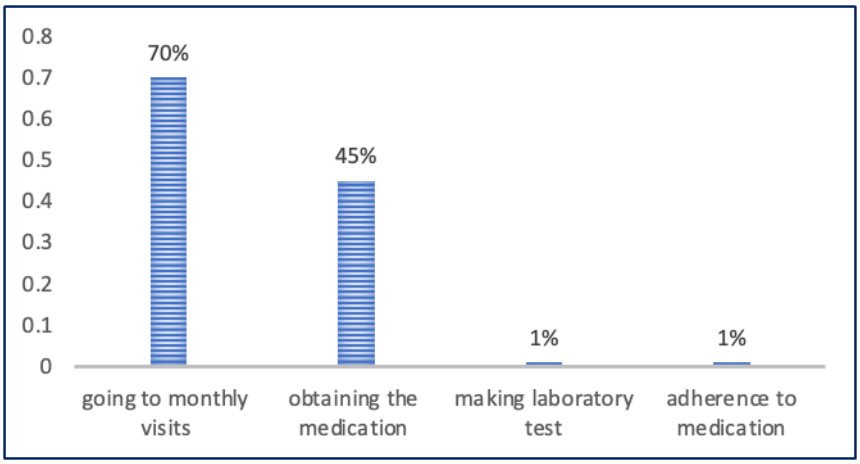

Figure 6: The effect of treatment with Coronavirus

9. Married Females' Participants

Married women received additional questions. There was a total of seven married women who participated in the study (5 women in the intervention group and 2 women in the control group. All of our sampled married female patients were non-pregnant (100%). Out of them, 71.5% (5 patients); 60% (3 patients) of the intervention group, and 100% (2 patients) of the control group used one type of contraceptive at baseline, after the education process for the intervention group and at follow-up, 100% of patients were using contraception. Referring to contraceptive use during isotretinoin therapy, 0% of the married women in the intervention group and 50% (one patient) in the control group used two different contraceptives. In contrast, after the education process for the intervention group and at follow-up, 100% of patients were using two methods of contraception.

Additionally, no one of the participants reported that they had a pregnancy test every month at baseline. At follow-up, 60% (3 patients) in the intervention group did the pregnancy test monthly compared to no one in the control group. 100% of the participants said that the physician informed them about the teratogenicity of isotretinoin, and they signed a pre-approval sheet before starting the treatment.

Informed consent

Appendix 1

Informed consent

This study aims to determine clinical pharmacist role in increasing adherence to recommendations among patients using isotretinoin in Jordan.

You are invited to participate in a research study to measure whether an active intervention (educational process) by the clinical pharmacist will increase the patient adherence to recommendations related to isotretinoin, awareness about proper use, and dealing with the side effects.

Participation in this study is completely voluntary, there are no known risks or inconveniences associated with this study. If you choose to be in study, you can withdraw at any time without adversely affecting your relationship with anyone at the University of Science and Technology. Your responses will be kept strictly confidential, and the data will be stored digitally only in secure files on computers. When any report on this research is available to the public, it will not include your name or any other individual information through which your identity can be identified.

If you have any questions about whether you were treated in an illegal or unethical manner, or if you have questions or want a copy or summary of the results of this study, you can contact the researcher, Dr Bushra Hijazi at her email bmhijazi3@just.edu.jo or Dr. Ruba Al Abdullah, at her
e-mail: Ruba.yousef1995@gmail.com

Feel free to take a copy of this approval page to keep it in your records. Choosing the "I agree" option below indicates that you are 18 years old or older and indicates your agreement to participate in this study.

◯ I agree ◯ I disagree

Appendix 2

Recommendations for managing side effects:

1- Recommended OTC products for the treatment of common adverse effects

Dry eyes: artificial tears and eye refreshments.

Dry mucus membranes and nose: saline nasal spray and Vaseline.

Dry lips: petroleum lip balm, nonmedicated lip balm.

Dry skin; glycerin-based or lactic acid moisturizing lotion or cream.

Sunburn: choose sunscreen with SPF15 or higher that doesn't contain para-aminobenzoic acid due to drying effect, [2] , and void excessive exposure to the sun because your skin may become more sensitive to sunlight while using the drug, and sunburn may increase [3].

*increase intake of water will decrease the dryness.

2- Isotretinoin causes an elevation of (AST), (ALT) liver enzyme, and (LDH), Triglyceride (TGA) lipid profile, also can lead to pancreatitis. Therefore, monitoring is essential to ensure the safe use of the product, so should be checked before treatment, one month after the start of treatment, then subsequently at three monthly intervals unless more frequent monitoring is indicated [4].

*Reduced intake of junk food and alcohol consumption will control the increase in lipid profile.

3- Female patients must always be informed about the teratogenic risk [5] and required to use two forms of contraception, starting one month before therapy and continuing for one-month post therapy[6]. Patients should be educated about appropriate forms of birth control since some types are unacceptable, such as the female condom and progesterone-only birth control pills (primary forms of birth control: tubal sterilization, vasectomy, intrauterine device, and combination hormonal therapy. Secondary structures of contraception: condoms, diaphragms, cervical caps, and vaginal sponges containing spermicide).

*they have to make monthly pregnancy test while taking isotretinoin.

To reduce fetal exposure to isotretinoin, Clinical pharmacists should encourage the use of iPLEDGE, a risk management program to regulate the use of isotretinoin, Available at https://www.ipledgeprogram.com/iPledgeUI/home.u, and its goal to ensure that women using isotretinoin do not become pregnant and women who are pregnant do not use isotretinoin.

4- Do not breastfeed while taking isotretinoin and for one month after stopping it. Isotretinoin may pass through the milk and harm the baby[7].

5- There are important warnings must be mentioned:

- vitamins :(do not take vitamin A),
- antibiotics: (Do not take tetracyclines, may increase the pressure in the brain with isotretinoin),
- lenses: (may make irritation), so avoid using it as much as possible
- blood donation: (It is not possible to donate blood for at least one-month post therapy for fear of giving your blood to a pregnant woman, causing congenital diseases in the fetus.),
- waxing and laser hair removal: may cause pigmentation and skin irritation, so it should be avoided during treatment and 6 months after stopping the drug(preferred).
- Cosmetics: (Do not use cosmetic procedures to smooth your skin; it may increase your chance of scarring or inflammation of the skin from these procedures). https://www.medicines.org.uk/emc/product/3870/pil (isotretinoin leaflet).

6- Isotretinoin may cause depression, psychosis, and violent behavior; particular care needs to be taken in a patient with a history of depression, and all patients should be monitored for signs of depression and referred for appropriate treatment if necessary. A further psychiatric or psychological evaluation may be necessary. (leaflet)

7- Take it with food or after food, and it prefers to take with fatty meals, store at room temperature. (leaflet)

8- Isotretinoin may cause pain in the muscles or joints, especially for adolescents who undergo vigorous exercise. Painkillers can be taken in this case, such as non-steroidal analgesics or paracetamol. (leaflet)

9- Do not use two doses at one time if you missed the dose (isotretinoin leaflet).

10 - Do not share isotretinoin with other people. It can cause congenital disabilities and other serious health problems. (leaflet)

11- Inform the doctor or pharmacist of any medicine that you will take during treatment with isotretinoin, because drug interactions may occur. (Leaflet)

Appendix 3

A. Baseline questionnaire

General information	
Age:	
Marital status: □Single □ Married	Gender: □ female □ Male
Educational level: □ Basic □ Secondary □ High school □ Diploma □ Bachelor □ Master □ PHD	
Residential area: □ Irbid □ Amman □ Al Zarqa □ Al Mafraq □ Al Balqaa □ Al Karak □ others, Mention	
Profession: □ Medical Profession □ Non-medical profession □ Student □ Doesn't work	Weight (Kg) Hight (cm)
Monthly income: □ less than 500 JD □ 500-1000 □ above 1000	
Do you have health insurance? □ yes □ No	
Current dose of isotretinoin medication: □ Number of capsules: □ number of times: □strength:	
Period since the initiation of isotretinoin medication: □ Newly diagnosed □1 month □ 2 months □ 3 months □ 4 months, others	

Please answer the following questions about your current of isotretinoin:

1. Do you have chronic diseases?

- Pressure
- Diabetes
- Thyroid gland

- Other……

2. Have you been asked for the following laboratory tests?

- Pregnancy test: - yes - no -not applicable
- Liver function test: - yes -no
- Lipid profile test: - yes -no

3. Did you make liver function test and lipid profile test before starting treatment?

- Yes
- No

4. Have you ever used isotretinoin without prescription even for one time?

- Yes
- No

5. Is it your first visit to a dermatologist to acne?

- Yes
- No

6. Did anyone explain to you about the medicine?

- Yes
- No

- Please specify who explained to you about the medicine?

- Doctor
- Pharmaceutical
- The doctor and the pharmacist.
- Otherwise.

7. How much does acne affect your daily, psychological and social life?

- Very big impact.
- Big impact
- Medium
- Weak
- There's no effect.

8. What do you think your acne is?

- Mild < 30 black and white pills
- Moderate ~ 100 black and white pills

- Severe nodules, big, painful red pills.
- Very severe (there are scar scars, pigments and old raisins)

Please answer the following knowledge questions:

9. Which of the following is isotretinoin side effect?

□ Dryness □ Teratogenicity □ Abnormal lipid profile
□ Constipation □ difficulty in breathing □ back pain □ Others

10. (In case of using isotretinoin based on medical prescription), the physician had explained for me isotretinoin side effects and how to manage them:

- Yes
- No

11. Isotretinoin can be used without prescription:

- Yes
- No
- I do not know

12. Isotretinoin can be used during some periods of pregnancy:

- Yes
- No
- I do not know

13. There is no need to have laboratory tests during isotretinoin therapy:

- Yes
- No
- I do not know

14. It is recommended to drink plenty of water during isotretinoin therapy to avoid dryness:

- Yes
- No
- I do not know

15. It is recommended to use sun block during isotretinoin therapy:

- Yes

- ☐ No
- ☐ I do not know

16. It is recommended to take isotretinoin after fatty meals:

- ☐ Yes
- ☐ No
- ☐ I do not know

17. Blood donation is allowed during isotretinoin therapy:

- ☐ Yes
- ☐ No
- ☐ I do not know

18. Breast feeding is allowed during isotretinoin therapy:

- ☐ Yes
- ☐ No
- ☐ I do not know

19. wax and laser for hair removal is allowed during isotretinoin therapy:

- ☐ Yes
- ☐ No
- ☐ I do not know

For married female. kindly answer the following questions

20. Do you use contraception method during your isotretinoin therapy?

- ☐ Yes
- ☐ No

21. Did you have pregnancy test before starting isotretinoin therapy?

- ☐ Yes
- ☐ No

22. Did your doctor explain for you the teratogenicity of isotretinoin?

- ☐ Yes
- ☐ No

23. Did the pharmacist explain for you the teratogenicity of the drug?

- ☐ Yes
- ☐ No

24. Did your doctor request you to sign up consent form which explain to you the isotretinoin side effects?

- ☐ Yes

□ No

25. (In case of using isotretinoin based on medical prescription), the doctor has explained to me the importance of using two contraceptive methods during isotretinoin therapy:

□ Yes
□ No

26. Do you think you needed to explain more about the drug in general?

□ Yes

□ No

27. Do you think you needed to explain more about the drug in terms of the method of use?

□ Yes

□ No

28. Do you think you need edited more explanations about the side effects of the drug and how to avoid it?

□ Yes

□ No

29. Do you have any feedback regarding this questionnaire?

□ Yes …….

□ No

Measure of the HADS score:

I'm frustrated.	**D**	**I feel confused.**	**A**
Always	3	Always	3
Often	2	Often	2
Sometimes	1	Sometimes	1
At all	0	At all	0
I'm scared.	**A**	**I still enjoy the things I used to enjoy.**	**D**
Always	3	Always	0
Often	2	Often	1
Sometimes	1	Sometimes	2
At all	0	At all	3
I lost interest in my appearance.	**D**	**I feel kind of afraid something bad is going to happen.**	**A**
Always	3	Always	3
Often	2	Often	2
Sometimes	1	Sometimes	1
At all	0	At all	0
I'd like to have fun and look forward to enjoying things.	**D**	**I can laugh and see the funny side of things.**	**D**
Always	0	Always	0

Often	1	Often	1
Sometimes	2	Sometimes	2
At all	3	At all	3
I suddenly feel shaking.	**A**	**Disturbing thoughts are in my mind.**	**A**
Always	3	Always	3
Often	2	Often	2
Sometimes	1	Sometimes	1
At all	0	At all	0
I can enjoy a book or tv show.	**D**	**I feel happy.**	**D**
Always	0	Always	0
Often	1	Often	1
Sometimes	2	Sometimes	2
At all	3	At all	3
I can sit down easily and feel comfortable.	**A**	**I feel unstable.**	**A**
Always	0	Always	3
Often	1	Often	2
Sometimes	2	Sometimes	1
At all	3	At all	0

B. Follow-up questionnaire

1. Have there been any changes in the dose? (Number of tablets / concentrate)

   - ☐ Yes
   - ☐ No

2. What are the results of previous tests?

   - ☐ LFT: - Normal - high - low
   - ☐ lipid profile: - normal -high -low

3. Have you been asked to do new tests for this month (after three months of treatment):

   - ☐ Pregnancy test: - yes - no -not applicable
   - ☐ Liver function test: - yes -no
   - ☐ Lipid profile test: - yes -no

4. Do you consult your doctor or pharmacist before using any other medications or dietary supplement during isotretinoin therapy?

   - ☐ Always 100%
   - ☐ often 70%

- Sometimes 50%
- Rarely 20%
- Never 0%

5. During your treatment period, did you seek help from outside sources for obtaining information about the medication?

   - Yes
   - No

   - What are the sources?

   - Internet
   - Social networking sites
   - Leaflet
   - Relatives or friends
   - Other……..

6. Do you have follow-up visits at regular basis with your physician?

   - Yes
   - No

   - If the answer is “Yes” for the previous question. kindly specify follow-up period:

   □ every month □ every two months

   □ every three months □ More than three months

7. In your opinion, how much is the improvement of your disease (acne)?

   - Excellent
   - Very good.
   - It's good.
   - Acceptable
   - Weak

Please answer the following knowledge questions:

8. Which of the following is isotretinoin side effect?

□ Dryness □ Teratogenicity □ Abnormal lipid profile
□ Constipation □ difficulty in breathing □ back pain □ Others

9. (In case of using isotretinoin based on medical prescription), the physician had explained for me isotretinoin side effects and how to manage them:

□ Yes
□ No

10. Isotretinoin can be used without prescription:

□ Yes
□ No
□ I do not know

11. Isotretinoin can be used during some periods of pregnancy:

□ Yes
□ No
□ I do not know

12. There is no need to have laboratory tests during isotretinoin therapy:

□ Yes
□ No
□ I do not know

13. It is recommended to drink plenty of water during isotretinoin therapy to avoid dryness:

□ Yes
□ No
□ I do not know

14. It is recommended to use sun block during isotretinoin therapy:

□ Yes
□ No
□ I do not know

15. It is recommended to take isotretinoin after fatty meals:

□ Yes
□ No
□ I do not know

16. Blood donation is allowed during isotretinoin therapy:

□ Yes
□ No
□ I do not know

17. Breast feeding is allowed during isotretinoin therapy:

- Yes
- No
- I do not know

18. wax and laser for hair removal is allowed during isotretinoin therapy:

- Yes
- No
- I do not know

For married female. kindly answer the following questions

19. Do you use contraception method during your isotretinoin therapy?

- Yes
- No

20. Did you have pregnancy test before starting isotretinoin therapy?

- Yes
- No

21. Did your doctor explain for you the teratogenicity of isotretinoin?

- Yes
- No

22. Did the pharmacist explain for you the teratogenicity of the drug?

- Yes
- No

23. Did your doctor request you to sign up consent form which explain to you the isotretinoin side effects?

- Yes
- No

24. (In case of using isotretinoin based on medical prescription), the doctor has explained to me the importance of using two contraceptive methods during isotretinoin therapy:

- Yes
- No

25. How well do you stick to the instructions to avoid medication-related side effects?

- Excellent
- Very good.
- It's good.
- Acceptable
- Weak

26. What is the impact of the side effects on your daily life and your usual activities?

- Big effect
- moderate effect

- Weak effect
- There's no effect.

27. Was the menstrual cycle affected during treatment?

- Yes
- No

- If yes, what is the impact?

- getting late
- getting early
- became heavy
- became light
- its duration became longer
- its duration became shorter

28. Was your treatment affected during the Corona period?

- Big effect
- moderate effect
- Weak effect
- There's no effect.

- If yes, what is the impact?

- Getting the medication
- adherence to medication
- Going for monthly doctor reviews
- adherence to periodic tests

29. Do you think you needed to explain more about the drug in general?

- Yes
- No

30. Do you think you needed to explain more about the drug in terms of the method of use?

- Yes
- No

31. Do you think you need edited more explanations about the side effects of the drug and how to avoid it?

- Yes
- No

32. Do you have any feedback regarding this questionnaire?

- Yes …….

□ No

Please answer the following questions regarding adherence to recommendations provided by clinical pharmacist.

	yes	no	I do not know	Not applicable
I adhere to drink plenty of water during isotretinoin use				
I adhere to use eye drop during isotretinoin use				
I adhere to use lip balm during isotretinoin use				
I adhere to use body lotion during isotretinoin use				
I adhere to make laboratory monitoring (AST & ALT) during isotretinoin				
I adhere to make lipid profile test during isotretinoin use				
I adhere to use sunblock when going out during isotretinoin use				
I adhere to take isotretinoin with fatty foods				
I adhere not to donate blood during isotretinoin use				
I adhere not to make laser or wax during isotretinoin use				
I adhere not to breastfeed my child during treatment:				
I adhere to do a monthly pregnancy test				

Please answer the following questions regarding adherence to the medication?

	At all	Rarely	Sometimes	Usually,	Always
Do you forget to take your meds?					
Do you skip medication when you feel better?					
Do you skip taking medications when they're worse after taking medications?					
Have you run out of your medications?					
In general, do you adhere to what your doctor or pharmacist tells you about your lifestyle (food, exercise, smoking...) I don't think					
Can you please tell us what are the most common reasons for not taking your medications?					

Measure of the HADS score:

I'm frustrated.	**D**	**I feel confused.**	**A**
Always	3	Always	3
Often	2	Often	2
Sometimes	1	Sometimes	1
At all	0	At all	0
I'm scared.	**A**	**I still enjoy the things I used to enjoy.**	**D**
Always	3	Always	0
Often	2	Often	1
Sometimes	1	Sometimes	2
At all	0	At all	3
I lost interest in my appearance.	**D**	**I feel kind of afraid something bad is going to happen.**	**A**
Always	3	Always	3
Often	2	Often	2
Sometimes	1	Sometimes	1
At all	0	At all	0
I'd like to have fun and look forward to enjoying things.	**D**	**I can laugh and see the funny side of things.**	**D**
Always	0	Always	0
Often	1	Often	1
Sometimes	2	Sometimes	2
At all	3	At all	3

I suddenly feel shaking.	**A**	**Disturbing thoughts are in my mind.**	**A**
Always	3	Always	3
Often	2	Often	2
Sometimes	1	Sometimes	1
At all	0	At all	0
I can enjoy a book or tv show.	**D**	**I feel happy.**	**D**
Always	0	Always	0
Often	1	Often	1
Sometimes	2	Sometimes	2
At all	3	At all	3
I can sit down easily and feel comfortable.	**A**	**I feel unstable.**	**A**
Always	0	Always	3
Often	1	Often	2
Sometimes	2	Sometimes	1
At all	3	At all	0