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Evaluation and orientation of isotretinoin side effects among a sample of Saudi population

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ABSTRACT

Introduction: Acne vulgaris is a common dermatological disorder in Saudi Arabia (KSA). Severe acne can be treated more affordably with isotretinoin, but there are a number of adverse effects to be cautious of. This study aims to identify the most prevalent isotretinoin side effects among Saudi citizens and assess how well-informed Saudis are about the drug. *Methods:* A longitudinal cohort study will be conducted using a pre-validated and translated electronic questionnaire and direct questions will be asked to the patient by meeting them in person, contacting them via mobile or social media. *Results:* This study found that 26% of 3953 people used isotretinoin, with most prescriptions being done by doctors (91%). 61.2% of participants were suffering from dryness of the body, with 61.1% suffering from dry eyes and 72.4% suffering from dry lips. 37% were aware that isotretinoin can cause birth abnormalities, while 88% of respondents used contraceptive pills, intrauterine devices (IUDs) where used by 18% from the participant while in 32% participant both contraceptive pills and isolation. In 88% of respondents, isotretinoin may help prevent pregnancy, with 50% using contraceptive pills, 18% using intrauterine devices (IUDs), and 32% using both pills and isolation. *Conclusions:* The study found that while isotretinoin adverse effects are common throughout the world, Saudi Arabians may not be fully aware of all of the medication's possible drawbacks. An orientation programme is needed to inform the community on the potential negative effects.

Keywords: Isotretinoin, acne, Saudi population, a long-term cohort investigation, KSA

1. INTRODUCTION

Isotretinoin taken orally has proven to be a major pharmacological breakthrough for treating severe and recalcitrant cases of inflammatory acne which in one local study show it is common dermatological disease reach 65% of total sample (Alshammrie et al., 2020). Several million patients, including a subset of children, have been treated with isotretinoin. Acne can be cured or nearly cured with isotretinoin based on clinical studies and global experience. The typical Muco-cutaneous adverse effects depend on the dose and can be managed with dose adjustment and/or extra symptomatic medication. One of

the most important potential side effects that are well understood is teratogenicity (Leyden et al., 2014).

Isotretinoin use has been linked to a number of musculoskeletal adverse effects, including arthralgia, myalgia, back discomfort, symptoms of spondyloarthropathy, and sacroiliitis (Alkan et al., 2015; Baykal-Selçuk et al., 2017; Stern, 1989). In a study conducted by Baykal-Selçuk et al., (2017), 73 individuals receiving isotretinoin for moderate to severe acne vulgaris were reviewed, and each patient was questioned regarding their inflammatory back pain and musculoskeletal problems. 42.5% of the patients experienced myalgia, while 49.3% of the patient had lower-back discomfort. 8.2% of them had acute sacroiliitis as determined by a sacroiliac MRI (Baykal-Selçuk et al., 2017).

In a different trial, Tetracycline or Isotretinoin was given to two groups of people with acne vulgaris in various methods. Spondyloarthropathy symptoms were reported by 23.1% of the participants in the isotretinoin group. The 32 patients in the tetracycline group did not experience any inflammatory back pain. Only one patient with unilateral sacroiliitis was found among the 42 patients who made up the isotretinoin group. They further stressed that the complaints were brought on by the medication and that after the treatment was terminated, all of the patients' rheumatologic symptoms disappeared (Alkan et al., 2015).

Another study looked into how isotretinoin affected Achilles tendinopathy. The researchers divided 16 rats into two groups, giving the first group isotretinoin and the second group soy oil. After six weeks, the Achilles tendons were extracted and histopathologically evaluated. It was discovered that the isotretinoin group's histology and biomechanics were adversely damaged (Beytemür et al., 2018). Studies have revealed that individuals with severe acne, particularly those who are teens and young adults, experience poorer quality of life and well-being, increased psychological discomfort and social anxiety, poor self-image, loss of self-esteem, and an increase in symptoms of anxiety, melancholy, and suicidal thoughts.

Other studies have shown that people with severe acne are more prone to experience concurrent depression and other psychological issues. In a different study, three patients using isotretinoin had sad mood, loss of interest, apathy, tearfulness, suicidal ideation, and a sense of worthlessness. Their HAM-D scores ranged from 26 to 31. After they stopped the isotretinoin and they took antidepressant the HAM-D score dropped in all patients to 7-9 with significant change in mood, which indicate a strong relation between isotretinoin and psychiatric changes (Barankin and De-Koven, 2002; Byrne et al., 1998; Chu and Cunliffe, 1999).

Sebaceous gland shrinkage, increased transepidermal water loss, skin barrier malfunction, and aberrant epidermal lipid production are the causes of isotretinoin's mucocutaneous side effects. Isotretinoin long term use results in xerosis, increased skin fragility, and an increased risk of frictional injury (Beytemür et al., 2018). Several studies report increases in serum TG of 25% of patients and in serum TC of 15% of patients, while other studies report serum TG increases of 5% to 18% and serum TC increases of 6% to 32. In follow-up studies of people using oral isotretinoin, TG, TC, and transaminase levels all increased by 5% to 44%, 6% to 31%, and 3% to 11%, respectively (Alcalay et al., 2001).

Follow-up research was undertaken on 70 patients who were receiving oral isotretinoin daily doses ranging from 20 milligrammes to 80 milligrammes, according to Vieira et al., (2012). These investigators indicated a mathematically crucial raise in the average (SD) amounts of triglycerides (87.01 (48.25) compared to 105.32 (48.76) milligram/dL), AST (20.44 (6.26) compared to 24.38 (11.92) IU/L) and ALT (18.24 (8.31) compared to 23.34 (20.03) IU/L) performed before and 3 months or more after the start of giving isotretinoin orally. 11% of the individuals had TG levels above normal after taking oral isotretinoin, while 7.3% and 8.6% of participants had raised ALT levls (Vieira et al., 2012).

A study found that early on, isotretinoin had no effect on the cornea or the conjunctiva of the globe, only the meibomian glands and the conjunctiva of the eyelids. Evaporative dry eye is the cause of the patients' symptoms, according to the initial isotretinoin signs on the eyelids, especially on the meibomian glands (Karadag et al., 2020). In a research, Isotretinoin was prescribed to patients with serious acne vulgaris to see how it would affect their pulmonary function tests (PFTs) and nasal mucociliary clearance. A 4-point scale was used to grade each side effect. The mucociliary clearance was measured using the saccharin test (ST). ST and PFTs were performed on each patient prior to and during the third month of treatment. There was a total of 40 acne sufferers.

Dehydration, chapped lips, and xerosis were the most frequent negative side effects. Of the 13 persons who reported minor epistaxis, only two had bleeding that was more than 10 cc in size. Forced vital capacity (FVC), forced expiratory volume in one second (FEV1), forced exhalation flow rate between 25% and 75% of FVC (FEF25-75), and their predicted percentage ratios were all the same before and after the third month of treatment. Treatment considerably extended the time it took for nasal clearance to occur, and there was an important association between drug dosage and mucociliary cell clearance. Isotretinoin interfered with mucociliary clearance and produced indications and symptoms of a dry nose without altering PFTs (Pile and Sadiq, 2023).

2. METHODS AND MATERIALS

Study Design

This study conducted between September 2022 to April 2023. This study is a prospective (cohort) one. The research population in Saudi Arabia comprised people of all ages. The categories were determined on account of the population's rapid uptake of isotretinoin and their frequent attendance at dermatology clinics and other clinics on account of the drug's numerous side effects. Sampling methods include anonymously approaching patients, calling them on their phones, and sending them online questionnaires.

Collection and processing of samples

This study will make use of an electronic questionnaire that has been pre-validated and translated. The questionnaire consists of four parts. The first part about the demographic data for the participant. Second part is about the isotretinoin prescription. The third section focuses mostly on the negative effects of isotretinoin, and the fourth section tests participant understanding of isotretinoin. Additionally, to ask the patient direct questions, the patient will be reached directly via phone, in-person meetings, texts, or social media platforms.

Utilising the statistical programme Statistical Package for Social Science (SPSS) version 24, the data was evaluated, coded, and then analysed. When necessary, sophisticated analysis methods like the t-test, ANOVA, and Chi-square will be employed to compare dependent and independent variables. Descriptive statistics, such as frequency and percentage for qualitative variables, mean and SD for quantitative variables, and mean and SD for qualitative variables were used to analyse the obtained data.

Ethical consideration

The University of Hail's research ethics committee gave their approval to this project. All participants gave their informed consent before participating in the research, and they were also made aware of its goals, of their right to withdraw from it at any time, and of the confidentiality and privacy of their data.

3. RESULTS

In this current study about 3953 individuals were enrolled, of whom, 75% were females, while men make up only 25% of participants; roughly 45% of participants are between the ages of 19 and 25; 24% are over 30; 18% are between the ages of 12 and 18; and 12% are between the ages of 26 and 30; the majority of participants were of Saudi nationality; just 10% of participants were from the south; 30% of participants were from the west; 26% from the north; and 19% from the middle; near to two-third of participants had university degree, the rest either completed secondary level (34%), or other certificates (8%); The bulk of participants (71%) were single (Table 1). The ongoing current study also found that most of Isotretinoin prescription was done by doctor (91%), the rest from Pharmacist, friends or their self, 29%, 3% or 2.5% respectively (Table 2).

Table 1 Participants' distribution based upon demographic characteristics N = 3953

Variable	Value	Fr	%
Gender	Male	984	24.9
	Female	2969	75.1
Age group in years	12 - 18	721	18.2
	19 - 25	1786	45.2
	26 - 30	478	12.1
	> 30	968	24.5
Nationality	Saudi	3704	93.7
	Non-Saudi	249	6.3
Region	North	1038	26.3
	East	559	14.1
	Middle	740	18.7
	West	1198	30.3
	South	418	10.6
Educational	Intermediate school	103	2.6

level	Secondary school	1325	33.5
	University	2469	62.5
	Post-graduate	25	.6
	Other	31	8
Marital status	Single	2818	71.3
	Married	1135	28.7

Table 2 Participants' distribution based upon on how much, when, and who prescribed the isotretinoin they used.

Variable	Value	Fr	%
Use of Isotretinoin	Yes	1024	26
	No	2929	74
	Total	3953	100
Dosage of Isotretinoin used in Mgs	10	182	17.8
	20	476	46.5
	30	226	22.1
	40	76	7.4
	50	49	4.8
	60	15	1.5
	Total	1024	100
Period of use per month	< 1	78	7.6
	1 – 3	290	28.3
	3 – 6	372	36.3
	More than 6	284	27.7
	Total	1024	100.0
Who prescribe of Isotretinoin	Doctor	933	91.5
	Pharmacist	30	2.9
	Friends and relatives	32	3.1
	My self alone	25	2.5
	Total	1020	100.0

About 61% of participants were suffering from complete dryness of the body; 61% were suffering from dry eyes; 72% were suffering from dry lips (Table 3). About 13% of participants were suffering from skin diseases such as eczema, 28% having redness or itching of the skin; 41% experiencing hair loss while you were using Isotretinoin; 36% suffered from changes in the psychological state or depression and about 11% of participants noticed a rise in liver enzymes after the lab tests (Table 4).

Table 3 Participants' distribution based upon whether they experience complete body, eye, or lip dryness

Variable	Value	Fr	%
Suffering from complete dryness of the body	Yes	622	61.2
	No	181	17.8
	Maybe	214	21.0
	Total	1017	100.0
Suffered from dry eyes	Yes	624	61.1
	No	269	26.3
	Maybe	128	12.5
	Total	1021	100.0
Suffer from dry lips	Yes	733	72.4
	No	173	17.1

	Maybe	107	10.6
	Total	1013	100.0

Table 4 Participants' distribution based upon those who have hair loss and skin conditions, changes in the psychological state or depression, or a rise in liver enzymes

Variable	Value	Fr	%
Suffering from skin diseases such as eczema	Yes	134	13.2
	No	833	81.9
	Maybe	50	4.9
	Total	1017	100.0
Having redness, or itching of the skin	Yes	286	28.0
	No	639	62.6
	Maybe	95	9.3
	Total	1020	100.0
Experiencing hair loss while you were using Isotretinoin	Yes	421	41.4
	No	394	38.7
	Maybe	202	19.9
	Total	1017	100.0
Suffered from changes in the psychological state or depression	Yes	366	35.9
	No	422	41.4
	Maybe	231	22.7
	Total	1019	100.0
Noticed a rise in liver enzymes after the lab tests	Yes	111	10.9
	No	760	74.5
	Maybe	149	14.6
	Total	1020	100.0

About 23% of participants had had gastrointestinal symptoms; 42% suffered from back, joint or bone pain; 40% noticed fatigue and lethargy while using Isotretinoin; 28% had a headache and 18% experienced dizziness or nausea (Table 5). Only 19% of participants' women mentioned that menstrual cycle affected while using Isotretinoin, while 14% of omen noticed an increase in hair growth on the body (Table 6).

Table 5 Participants' distribution based upon whether they experience stomach tremors, back, joint or bone pain, fatigue, headache, dizziness or nausea

Variable	Value	Fr	%
Had gastrointestinal symptoms	Yes	232	22.9
	No	644	63.6
	Maybe	137	13.5
	Total	1013	100.0
Suffered from back, joint or bone pain	Yes	428	42.0
	No	451	44.3
	Maybe	140	13.7
	Total	1019	100.0
Noticed fatigue and lethargy while using Isotretinoin	Yes	404	39.7
	No	432	42.4
	Maybe	182	17.9
	Total	1018	100.0
Had a headache	Yes	284	28.0
	No	541	53.4

	Maybe	189	18.6
	Total	1014	100.0
Experienced dizziness or nausea	Yes	182	18.0
	No	697	68.9
	Maybe	132	13.1
	Total	1011	100.0

Table 6 Participants' distribution based upon effects of using Isotretinoin for woman

Variable	Value	Fr	%
For women: Was your menstrual cycle affected while using Isotretinoin	Yes	164	18.5
	No	587	66.3
	Maybe	134	15.1
	Total	885	100.0
For women: Noticed an increase in hair growth on the body	Yes	123	13.7
	No	638	71.1
	Maybe	136	15.2
	Total	897	100.0

85% of interviewees have heard of acne; Isotretinoin is used to treat acne, according to 66% of people; 41% are knowledgeable about the dangers of isotretinoin; 56% are aware that the body becomes entirely dry while using isotretinoin; Knowing that isotretinoin can cause dry eyes, 46%; compared to 26% who are aware, 76% of persons do not wear eyeglasses while taking isotretinoin. 45% are aware that testing liver enzymes and cholesterol levels is required before using isotretinoin; 31% are aware that isotretinoin elevates liver enzymes; 34% of you are aware that isotretinoin can lead to mental health issues including depression; 38% and 18% of people are aware that isotretinoin causes skin irritation and redness, respectively (Table 7).

Table 7 Participants are arranged according to how well they comprehend how to use isotretinoin and its drawbacks.

Variable	Value	Fr	%
Do you know what acne is?	Yes	2466	84.6
	No	115	3.9
	Maybe	334	11.5
	Total	2915	100.0
Do you know that acne is treated with Isotretinoin?	Yes	1933	66.2
	No	706	24.2
	Maybe	280	9.6
	Total	2919	100.0
Do you know what isotretinoin's negative effects are?	Yes	1185	40.6
	No	1351	46.3
	Maybe	384	13.2
	Total	2920	100.0
Do you know that Isotretinoin causes complete dryness of the body?	Yes	1626	55.6
	No	1107	37.9
	Maybe	191	6.5
	Total	2924	100.0
Do you know that Isotretinoin causes dry eyes?	Yes	1339	45.9
	No	1388	47.6
	Maybe	188	6.4
	Total	2915	100.0
Do you know that wearing eyeglasses is not suggested	Yes	754	25.9
	No	1949	67.0

when taking isotretinoin?	Maybe	207	7.1
	Total	2910	100.0
Do you know that it is compulsory to check liver enzymes and lipid before using Isotretinoin?	Yes	1297	44.6
	No	1298	44.6
	Maybe	316	10.9
	Total	2911	100.0
Do you know that Isotretinoin causes an increase in liver enzymes?	Yes	896	30.8
	No	1681	57.8
	Maybe	333	11.4
	Total	2910	100.0
Do you know that Isotretinoin causes depression and mental health disorders?	Yes	997	34.4
	No	1575	54.3
	Maybe	327	11.3
	Total	2899	100.0
Do you know that Isotretinoin causes eczema?	Yes	521	18.0
	No	2030	70.0
	Maybe	351	12.1
	Total	2902	100.0
Do you know that Isotretinoin causes skin irritation and redness?	Yes	1117	38.4
	No	1429	49.1
	Maybe	365	12.5
	Total	2911	100.0

Table 8 Distribution of participants' woman according to Isotretinoin use and its side effects to birth, pregnancy and their practices for preventing pregnancy

Variable	Value	Fr	%
Are you aware that Isotretinoin causes birth defects?	Yes	1070	36.7
	No	1472	50.5
	Don't know	370	12.7
	Total	2912	100.0
If you are married and take Isotretinoin, is pregnancy occurs during or shortly after using Isotretinoin?	Yes	101	12.0
	No	746	88.0
	Total	847	100.0
If you are married, how many methods did you use to prevent pregnancy?	Contraceptive pills	315	50.0
	Intrauterine devices (IUDs)	109	18.0
	Contraceptive pills and isolation	200	32.0
	Total	624	100.0

Among participants, just 37% were aware that isotretinoin causes birth abnormalities, whereas 50% were ignorant of this fact; 88% mentioned that use of Isotretinoin may prevent pregnancy occurrence; for preventing pregnancy or family planning, about 50% used contraceptive pills, 18% used intrauterine devices and 32% used both contraceptive pills and isolation (Table 8).

4. DISCUSSION

We discovered that while the adverse effects of isotretinoin in our trial were comparable to those in other studies, there was significantly less awareness of the adverse effects than in the other studies. For instance, more than fifty percent of the participants were not aware that it is not advisable to use isotretinoin while pregnant. When compared to other techniques for managing acute forms of acne, isotretinoin is more affordable for treating people with acute acne (Bagatin et al., 2020). Consumers need to know that it has been demonstrated to have several major negative consequences, including teratogenic ones (Layton, 2009; Pile and Sadiq, 2023).

Therefore, the current study— first of its sort in the region of the north — assessed female acne patients' awareness of the usage of isotretinoin and its negative effects. According to this study, 26% of participants used isotretinoin on a regular basis. This result was lower than that of a previous study by Alshaalan, (2022), which revealed that 32% of individuals used it on a regular basis. The current study also found that most of Isotretinoin prescription was done by doctor (91%), the rest from pharmacist, friends or their self, 29%, 3% or 2.5% respectively. Our results are in line with a few previous KSA research (Albadr et al., 2019; Bakheet et al., 2020).

These ecological findings point to the necessity for SFDA-PPP awareness-raising programmes beyond consumers (acne patients taking isotretinoin), as well as an improvement in community chemists' understanding of isotretinoin policy (Rashid et al., 2020). Our study also found that about 61% of participants were suffering from complete dryness of the body; 61% were suffering from dry eyes; 72% were suffering from dry lips. Our results are consistent with earlier research done in the KSA and other parts of the world (Kara-Polat et al., 2020; Tugrul-Ayanoglu et al., 2019; Younis and Al-Harbi, 2019).

The majority of participants in this study (85%) are aware of what acne is; The use of isotretinoin to treat acne is known to 66% of people; 41% are aware of the risks associated with isotretinoin; 56% are aware that isotretinoin causes the body to become completely dry; 46% are aware that isotretinoin can result in dry eyes; 26% are aware that wearing eyeglasses while taking isotretinoin is prohibited, whereas 67% are unaware of this; 45% are aware that testing liver enzymes and cholesterol levels is required before using isotretinoin; 31% are aware that isotretinoin elevates liver enzymes; 34% you know that Isotretinoin causes depression and mental health disorders; 18% know that Isotretinoin causes eczema and 38% know that Isotretinoin causes skin irritation and redness. These findings diverge from those of another study by Younis and Al-Harbi, (2019).

The study's final findings showed that just 37% of participants knew that isotretinoin causes birth abnormalities; Isotretinoin use may help prevent pregnancy, according to 88% of respondents; for preventing pregnancy or family planning, about 50% used contraceptive pills, 18% used intrauterine devices and 32% used both contraceptive pills and isolation. Our findings are align with previous studies conducted (Al-Harbi, 2010).

5. CONCLUSION

The goal of the current study was to determine if female acne patients in the reproductive age range were aware of the uses, precautions, and side effects of isotretinoin, particularly its teratogenic unfavourable effects. Therefore, it is essential to increase the understanding of female acne sufferers through health promotion activities, notably thorough teaching about the teratogenic consequences of isotretinoin must be offered. We discovered that the participants had a poor level of awareness about SFDA-PPP operations.

We also revealed that nearly a third of the engaged participants did not get the SFDA-PPP guidelines on pregnancy tests and suggested methods of contraception. The appropriate authorities must therefore carry out initiatives to raise public awareness of the SFDA-PPP and its activities. All females in the reproductive age range, including acne sufferers, should be the target audience for these efforts. The current study also aimed to investigate how patient characteristics affect patients' knowledge of dangers. The current study's findings indicate the need for more research including the two other SFDA-PPP stakeholders, chemists and doctors.

Authors' contribution

Each author contributed to the data analysis and interpretation, and they all contributed to the final draft's critical review and approval. They are also each accountable for the manuscript's content and similarity score.

Ethical approval

This study was approved by the research ethic committee, University of Hail, Saudi Arabia (H-2023-127).

Authors' Contributions

All authors share in analyzed and interpreted data, also they have critically reviewed and approved the final draft and are responsible for the content and similarity index of manuscript.

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Conflict of interest

The authors declare that there is no conflict of interests.

Data and materials availability

All data sets collected during this study are available upon reasonable request from the corresponding author.

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