The Impact of Oral Isotretinoin Dryness and Depression on Saudi Women in Qassim Region: A Survey
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Abstract
Background: Oral Isotretinoin is the most effective choice in the treatment of severe acne. There is relationship between the use of Isotretinoin and depression and dryness.

Objectives: To assess the impact of oral Isotretinoin dryness and depression on saudi women in Qassim Region.

Method: This non-interventional cross-sectional survey was conducted between October 13 to November 8, 2015 in acne patients from the Qassim region. Online-based questionnaire used as study tool. The filled questionnaires were analyzed using SPSS version 21.

Result: A sample of 202 participants were obtained, most of them were of age group 18-25 years (75.7%). About 6% of females used the drug without consult the doctor. Only (28.2%) of participants did not suffer from side effect. Large number of participant said that they have crying episode during the treatment (about 27% of the participants). Almost all participants 198 females (98%) suffer from dryness. Seventeen percent of participants discontinue the treatment because of side effects.

Conclusion: Considerable number of Isotretinoin treated patients showed deferent signs of depression and this supports the association of Isotretinoin and depression. The dryness which is the major side effects of Isotretinoin appear in almost all females treated with Isotretinoin. No correlation found between dryness and any sign of depression.

Keywords: Isotretinoin; Depression and dryness; Severe acne

Introduction
Acne is a chronic inflammatory disease of the pilosebaceous units, and is primarily seen in adolescents. It can have a significant psychological and social impact. Most cases of acne present with a pleomorphic variety of lesions consisting of comedones, papules, pustules and nodules, and in some cases are accompanied by scarring [1].

Acne arises from the interaction of four factors: Comedogenesis—sebaceous follicle obstruction arising from increased cohesiveness of follicular epithelial cells, hyperproliferation of ductal keratinocytes, or both [2]. Excessive sebum production caused by androgenic stimulation of sebaceous glands at or around adrenarche or later [3]. Proliferation of Propionibacterium acnes, an anaerobic diphtheroid that populates sebaceous follicles and is a normal constituent of cutaneous flora. P. acnes produces chemotactic factors and proinflammatory mediators that may lead to inflammation [4]. Inflammation is a direct or indirect result of P. acnes proliferation. Follicular rupture and extension of inflammation into the dermis result in formation of the inflammatory lesions of acne vulgaris—papules, pustules, and nodules [3].

Correct classification of lesion type is essential for choosing the most effective therapy. The severity grades assigned (mild, moderate, severe) are based on lesion count approximations. The term severe acne may be applied if ongoing scarring or persistent lesion drainage is involved or if sinus tracts are present. In addition, the most destructive forms of acne—acne conglobata, acne fulminans, follicular occlusion triad—are classified as very severe [3].

Retinoids are a key component of anti-acne therapy. The introduction of Isotretinoin, a first generation synthetic retinoid, for the treatment of patients with moderate to severe acne vulgaris is regarded as a major therapeutic advance in dermatology [5].

Oral Isotretinoin (13-cis retinoic acid (RA)) belongs to retinoid, a group of compounds derived from the essential nutrient vitamin A, which performs a large number of functions in many systems among them the central nervous system (CNS) [6].

Dates back to 1979, when its successful use for patients with cystic and conglobate acne. (Peck et al.) treated 14 patients with an average of 2.0 mg/kg daily, and noted 75-100% improvement with prolonged remission in all patients [7].

Oral Isotretinoin approved by the United States (US) Food and Drug Administration (FDA) as an oral capsule formulation in May 1982 with an indication for treatment of severe recalcitrant nodular acne [8].

Oral Isotretinoin was first introduced in Saudi Arabia late in 1987. In last 7-year retrospective study, efficacy and side effects of Isotretinoin are reviewed in Saudi patients with acne vulgaris seen in a university skin clinic in Riyadh, Saudi Arabia [9].

Isotretinoin reduces sebaceous gland size and inhibits sebaceous gland activity, thereby decreasing sebum secretion. This action is probably responsible for the rapid initial clinical improvement in nodular acne. Isotretinoin also has been shown to decrease the number of Propionibacterium acnes organisms within the follicle. However, since Isotretinoin has no effect on P. acnes in vitro, this action is probably a secondary effect due to decreased sebum secretion and the

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resulting decrease in nutrients and not a direct effect of Isotretinoin. In addition, Isotretinoin has been shown to have anti-keratinizing and anti-inflammatory actions. The exact role of these actions in clinical improvement of nodular acne is not known, especially with respect to prolonged remissions [8,10-12].

Low dose Isotretinoin — Doses of Isotretinoin lower than 0.5 mg/kg/day may be effective for the treatment of some patients with acne [13,14]. In a 24-week single-blind randomized trial, 60 patients with moderate acne were treated with one of three regimens of Isotretinoin: 0.5 to 0.7 mg/kg/day (higher dose regimen), 0.25 to 0.4 mg/kg/day (lower dose regimen), or 0.5 to 0.7 mg/kg/day for one week for every four weeks (intermittent regimen) [14]. All three treatment courses resulted in clinically significant improvement. The lower dose and higher dose regimens were similarly effective and had equivalent rates of relapse after one year; however, more adverse effects were reported in the higher dose group during treatment. A lesser degree of improvement and a lower duration of effect were detected in the patients who received intermittent therapy. The results of this trial suggest that treatment with less than 0.5 mg/kg/day of Isotretinoin is as effective as a slightly higher dose regimen in patients with moderate acne and is associated with fewer adverse effects. Of note, the study excluded individuals with severe acne, a group of patients for which Isotretinoin therapy is frequently indicated [15].

High-dose Isotretinoin — There is some evidence that high cumulative doses of Isotretinoin may reduce the risk of relapse in patients with severe acne vulgaris [16,17]. A prospective observational study of 180 patients with severe nodular acne resistant to other therapies found significantly lower rates of relapse one year after treatment cessation among patients who received a cumulative dose of Isotretinoin ≥ 220 mg/kg than those who received lower cumulative doses; 26.9 percent (95% CI 18.3-37.8 percent) versus 47.4 percent (95% CI 32.3-63.0 percent) relapsed, respectively [16]. After adjustment for age, sex, race, treating clinician, and duration of treatment, the difference in the proportion of patients who relapsed remained wide, but was no longer statistically significant (26.6 percent (95% CI 24.1-6.57 percent) and 43.8 percent (95% CI 16.3-40.3 percent), respectively). High-dose Isotretinoin appeared to be well-tolerated; retinoid dermatitis was the only side effect that occurred significantly more often in the ≥220 mg/kg Isotretinoin group (53.8 versus 31.6 percent). Additional studies are needed to confirm the results of this study as well as the safety of high-dose Isotretinoin therapy [15].

Oral Isotretinoin has a wide spectrum of side effects, including reproductive, Mucocutaneous, ocular, neurological, musculoskeletal, and hepatic. Some of which can result in very disastrous consequences like teratogenicity [18].

Mucocutaneous side effects of Isotretinoin, including cheilitis, dry skin and mucous membranes, epistaxis, desquamation, photosensitivity, and pruritus, are predictable and dose-dependent. The cheilitis can be significant and often requires the liberal use of topical emollients. Patients also have an increased risk of ocular symptoms such as dryness and irritation relating to dysfunction of meibomian glands within the conjunctiva [19,20] and cutaneous staphylococcal infections [21]. Paronychia, pyogenic granulomas, temporary diffuse alopecia, or nail brittleness may occasionally appear [22].

Dryness is the most common side-effect of oral Isotretinoin. Most patients experience harsh dryness, especially around the lips and eyes [23].

Psychiatric effects Concerns have been raised about a possible association of Isotretinoin with depression and suicide. Isotretinoin has been in the top 10 drugs reported to the FDA’s Adverse Event Reporting System for depression and suicide attempts [24]. Between the time Isotretinoin was marketed in 1982 and January 2005, the FDA received reports of 190 patients in the United States treated with Isotretinoin who committed suicide [25]. If there were no association between Isotretinoin and suicide, 220 suicides would have been expected in users of Isotretinoin in the US between 1982 and 2002, while there were actually only 165 suicides reported to the FDA in that time frame [25]. However, not all such suicides would have been reported to the FDA so the interpretation of these numbers is uncertain [15].

A case-crossover study was performed among subjects who received more than or equal 1 Isotretinoin prescription from 1984 through 2003. Data were obtained from the Régie de l’Assurance Maladie du Québec (RAMQ) and Quebec’s hospital discharge (Med-Echo) administrative databases. To determine whether Isotretinoin increases the risk of depression in patients with acne vulgaris, Azoulay et al. take 30,496 subjects in the initial cohort. The crude relative risk for those exposed to Isotretinoin was 2.00 (95% CI = 1.03 to 3.89). After adjusting for potential time-dependent confounders, the relative risk for those exposed to Isotretinoin was 2.68 (95% CI = 1.10 to 6.48). This is the first controlled study to find a statistically significant association between Isotretinoin and depression. Because depression could have serious consequences, close monitoring of Isotretinoin users is indicated [26].

The FDA reported 431 adverse drug reactions (ADRs) for Isotretinoin between the years 1982 and 2000. Of these 37 had committed suicide, 110 were hospitalized for either depression, suicidal ideation, or suicide attempts while 284 suffered depression without hospitalization. The Adverse Events Reporting System (AERS) database placed Isotretinoin as the 5th ranking drug for reports of serious depression, 4th ranking for depression. For attempted suicide Isotretinoin ranks number 10 and it is the only nonpsychiatric drug that ranks in this top ten lists. A study of the ADRs from the FDA also suggests a challenge/dechallenge effect for Isotretinoin with remission of depression resulting between cessation and restarting the drug. When the 2002 FDA reports were examined 3104 cases of psychiatric adverse effects were found for Isotretinoin, 173 of which were suicides [27] in 2012, an extensive review (until 2010) on Retinoic acid and affective disorders. Bremner et al. have outlined a relationship between Isotretinoin and depression. The evidence included case reports, temporal association between onset of depression and exposure to the drug, challenge-rechallenge studies (depression resolved after discontinuation of the drug and in some cases returned with its reintroduction), dose response, biologic plausibility and class effect (review of neuropsychiatric effects of hypervitaminosis A). Moreover, they reported that the incidence of depression in large studies of Isotretinoin-treated patients ranges from 1% to 11% [28].

A non-interventional cross-sectional survey in in Qassim 2010 To assess knowledge, concerns and awareness of acne patients in Qassim region, Saudi Arabia, about Isotretinoin. Al-Harbi takes 156 as study population. 63% of subjects knew about the adverse effects of the drug. Dryness and teratogenicity were the most well-known adverse effects and 85.9% didn't have any objection in using the drug. This study highlighted the importance of health education for better acceptance of this drug. Patients should be instructed about proper moisturization methods while using this drug [29].

Prospective, non-comparative study in Indian 2014 to evaluate safety and efficacy of low-dose isotretinoin in the treatment of moderate to severe acne vulgaris. Parinitha et al. take 50 as study population.
Cheilitis was the most common among the side effects observed and was seen in 98% of the participants. One participant developed vitiligo as a side effect, which is a new finding, and has not reported in literature before. Three months of treatment with low-dose Isotretinoin (20 mg/day) was found to be effective in the treatment of moderate to severe acne vulgaris, with a low incidence of serious side effects [30].

A Retrospective cohort study conducted in Israel 2012 to examine whether Isotretinoin therapy could result in deleterious ocular effects. Neudorfer et al. take 14682 as study population. They found that 13.8% of the Isotretinoin group experienced ocular effects compare with 9.6% of the Isotretinoin-naive group. The study [conclude that] Isotretinoin use may result in detersive ocular effects [31].

This study was done to assess Isotretinoin dryness and depression on Saudi females and to correlate this two side effects to each other.

Methodology

Materials

Study design: A national cross-sectional survey using Online-based questionnaire was conducted on Saudi young women in Qassim region aged 18-30 years old.

Study area and population

Study area: In Saudi Arabia, Qassim region.

Study Population: Saudi young women 18-30 years old.

Inclusion criteria:
- Saudi young women in Qassim region age between 18 to 30 years old.

Exclusion criteria:
- Non Saudi young women.
- Saudi young women in Qassim region age under 18 or above 30.
- Saudi young women not in Qassim region.

Sampling technique

Procedure: The online version was made using Google Forms and distributed via social media. The questionnaire form is attached (Appendix), filled by participants and then collected.

Sample size: A total is 202 young women in Qassim region.

Instrument of Data Collection

Questionnaire: The questionnaire consists of 22 was mainly composed of three sections. Section one consisted of ten items, mainly focusing on the demographics and common questions about the drug. The focus of section two was to assess the depression side effect which was consisted of six items. Section three was the last section of the questionnaire and aimed to assess the dryness side effect which was consisted of six items. The questions administered in Arabic, and of about 10 minutes long to fill. The surveys were conducted between, October 13 to November 8, 2015.

Methods

Pilot Study: A piloting survey of questionnaire was conducted in 10 young woman using online questionnaire to examine the questions, regarding the simplicity and understanding of questions. As a result of this pilot survey no modification was done for the questionnaire and accordingly data collection started.

Data analysis: After data collection, the date will be analysis using Statistical Package for the Social Sciences (SPSS) program version 21. For statistical significance, a P value of this test is (P<0.05). Then, the results will be discussed.

Results

Characteristics of participants

A total of 202 questionnaires online-based, were collected. Table 1 shows demographics of participants. Most participants were of age group 18-25 years old (75.7%). Accordingly most of them are undergraduate students (76.2%), (12.9%) High school students, (8.4%) Postgraduate students and 2.5% below high school.

| Variable   | N   | %    |
|------------|-----|------|
| Age        |     |      |
| 18 - 25    | 153 | 75.7 |
| 25 - 30    | 49  | 24.3 |
| Education  |     |      |
| Below high school | 5 | 2.5 |
| High school student | 26 | 12.9 |
| Undergraduate students | 154 | 76.2 |
| Postgraduate students | 17 | 8.4 |

Table 1: Demographics of participants.
Nearly 31 females (17.6%) discontinue the treatment, 13 females from them because they could not tolerate the side effects (Figures 6 and 7).

**Depression**

Large number of participant said that they have crying episode during the treatment (about 27% of the participants) (Figure 8).

Even more 39% of female said they had feeling of anger and do not like to speak, and 28% like to be isolated & site alone (Figures 9 and 10).

During the treatment 19% of participants females said they suffered from melancholy thought to their self and others (Figure 11).
According to results sleeping pattern is also affected during the treatment as more than 25% of participant had sleeping disorder (Figure 12).

**Dryness**

Almost all participants 198 females (98%) suffer from dryness (Figure 13).

The dryness appears mainly on the lips (68%), joint & hands equally (8.1%), less amount on eyes 15 participants (7.6%) (Figure 14).

Unfortunately many female (19%) did not get advice from physician or pharmacist to use the moisturizing cream (Figure 15).

Any way regardless if they advised or not, 155 (77%) female from the total participants said they used the moisturizing cream but others did not moisturize their body during the treatment (23%) (Figure 16).

Among those females suffer from dryness, 72% said dryness persist up to the end of treatment (Figure 17).

Moisturizing the body found to be beneficial for most female (84%) (Figure 18).

**Discussion**

The study was done to assess the adverse effects and its impacts of oral Isotretinoin specifically dryness and depression on young Saudi females. A total of 202 online based questionnaires were filled (Table 2).

It was found that 75.7% of respondents in the age group (18-25) years; this high percent indicate that most females use this drug in this age although the typical age of acne flare up is during adolescence (12-18). Most participants are undergraduate students 76.2% which consistent with percentage of age group.

Although Isotretinoin is prescription drug, the results indicate that considerable amount (6%) of participants used this drug without any consultation and half of them (50%) did not heard about the side effects of the drug.

In our study the 71.8% suffer from side effect as general without specification while in other retrospective study conducted in Australia (2010) by Australian college of dermatology, it was found that the total percentage of female suffered Isotretinoin side effects are 81.5% this difference may be due to genetic variation or it may arise as result of greater difference in the sample size. Six percent of our participants discontinued oral Isotretinoin because they could not tolerate the
insomnia or increase in sleeping pattern. Although all founded studies found that 25% they had sleep disorder without specification is it is one sign of depression, we assess this sign in our study and it was of patient had insomnia mainly [33]. As insomnia and sleep disorder only 5.5% develop this sign of depression. The same determined 7% treatment, while in one series of 110 Isotretinoin treated patients twenty seven percent of respondents had crying spells during the treatment period to sit alone and isolate. In our study hospitalized depression, and 37 patients committed suicide [24].

Although study only 18.5% from those prescribed the drug did not know the side effects while in Australian study only 1.5% stopped the drug due to the same reason. It is observable that this 6% is typically equal to those who used the drug without consultation. We suggest that the high percentage of participant discontinued the drug comparing to the Australian study (only 1.6), because of those used the drug as non-prescription [32].

In cross-sectional survey done in Qassim region 2010, it was found that 37% did not know adverse drug reaction of Isotretinoin. In our study 16% of patients suffer of transient arthralgias [35]. Eyes also dry during treatment period to sit alone and isolate. While in old study 16% of patients suffer of transient arthralgias [35]. Eyes also dry during treatment period to sit alone and isolate. Also in Indian study cheilitis is the most common dryness (cheilitis) represent high percentage. Our study found 68.2% showed symptoms or suicidal risk caused by Isotretinoin [34].

Dryness is the major ADR of Isotretinoin and almost all treated patients suffer from dryness. Our study also found 98% had dryness. The area of dryness is differing considerably but lip dryness (cheilitis) represent high percentage. Our study found 68.2% showed cheilitis. Also in Indian study cheilitis is the most common dryness (98%) [30]. Hand and joint another area of dryness. In our study both represent equal percentage of dryness (8%).While in old study 16% of patients suffer of transient arthralgias [35]. Eyes also dry during Isotretinoin use (7.6%) of our participants show eyes dryness. In European study comparing different doses of the drug they found the eye dryness is dose related [36].

This study also searched for correlation between the dryness and depression but the results give no significance at 95% confidence. This indicates that the two major side effects of Isotretinoin (dryness and depression) occur separately.

Table 2: Correlations.

| Dryness | Did you suffer from Melancholy thoughts about yourself and other | Did you suffer from feelings of upset anger and between antitogos | Did you suffer from sleeping disorders during the treatment period to sit alone and isolate | During the treatment period to sit alone and isolate | Suffer from feelings of anger during the treatment period | Suffer from episode of crying during the treatment period | Pearson Correlation | Sig. (2-tailed) |
|---------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-----------------|--------------|
| 0.07    | 0.445**                                        | 0.585**                                        | 0.301**                                        | 0.630**                                        | 0.581**                                        | 0.581**                                        | Pearson Correlation | Sig. (2-tailed) |
| 0.920   | 0.000                                          | 0.000                                          | 0.000                                          | 0.000                                          | 0.000                                          | 0.000                                          | -                | N             |
| 0.041   | 0.393**                                        | 0.491**                                        | 0.456**                                        | 0.647**                                        | 1                                              | 0.581**                                        | Pearson Correlation | Sig. (2-tailed) |
| 0.561   | 0.000                                          | 0.000                                          | 0.000                                          | 0.000                                          | 0.000                                          | 0.000                                          | N                | N             |
| 0.010   | 0.486*                                         | 0.563*                                         | 0.360*                                         | 1                                              | 0.647**                                        | 0.630**                                        | Pearson Correlation | Sig. (2-tailed) |
| 0.886   | 0.000                                          | 0.000                                          | 0.000                                          | -                                              | 0.000                                          | 0.000                                          | N                | N             |
| 0.002   | 0.412*                                         | 0.331*                                         | 1                                              | 0.360*                                         | 0.456*                                        | 0.301**                                        | Pearson Correlation | Sig. (2-tailed) |
| 0.973   | 0.000                                          | 0.000                                          | 0.000                                          | 0.000                                          | 0.000                                          | 0.000                                          | N                | N             |
| 0.025   | 0.387*                                         | 1                                              | 0.331*                                         | 0.563*                                         | 0.491**                                        | 0.585**                                        | Pearson Correlation | N             |
| 0.728   | 0.000                                          | 0.000                                          | 0.000                                          | 0.000                                          | 0.000                                          | 0.000                                          | Pearson Correlation | N             |
| 0.068   | 1                                              | 0.387*                                         | 0.412*                                         | 0.486*                                         | 0.393*                                        | 0.445*                                        | Pearson Correlation | N             |
| 0.333   | 0.000                                          | 0.000                                          | 0.000                                          | 0.000                                          | 0.000                                          | 0.000                                          | Pearson Correlation | N             |
| 0.068   | 0.068                                          | 0.025                                          | 0.002                                          | 0.010                                          | 0.041                                          | 0.007                                          | Pearson Correlation | N             |
| 0.333   | 0.728                                          | 0.973                                          | 0.886                                          | 0.561                                          | 0.920                                          | 0.920                                          | Pearson Correlation | N             |
| 0.202   | 0.202                                          | 0.202                                          | 0.202                                          | 0.202                                          | 0.202                                          | 0.202                                          | N                | N             |
| 0.202   | 0.202                                          | 0.202                                          | 0.202                                          | 0.202                                          | 0.202                                          | 0.202                                          | N                | N             |

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Limitation

The study has some limitation. The sample size selected only from Qassim region, moreover most participants are of age group of 18-25. The study was conducted using online based form only which has less protection against misuse. Also the online based form usually filled by peoples with certain level of education, less educated and uneducated females usually unable to use this form. Furthermore, since the used design and methodology in our study seems a little bit intuitive, we are going to enhance it as one of our future works. Lastly the study conducted using retrospective data which depend on the participants recall.

Conclusion

Isotretinoin used by some female without prescription and many of them did not hear about it is side effects. Considerable number of Isotretinoin treated patients showed deferent signs of depression and this supports the association of Isotretinoin and depression. The dryness which is the major side effects of Isotretinoin appear in almost all females treated with Isotretinoin. Although the location of dryness is differ from female to other but the lips is the more affected area. The ADR of Isotretinoin in some patients become intolerable and led to discontinuation of treatment. There is no association between dryness and any sign of depression.

Recommendations

1. Isotretinoin should be reserved only for treatment of severe acne.
2. All females prescribed oral Isotretinoin should inform oral Isotretinoin should inform about it is side effects.
3. All females using Isotretinoin should advise to use moisturizing cream.
4. When dispensing oral Isotretinoin pharmacists should counsel the females about the side effects and advise them to inform their dermatologist about any suspected side effects and mood change.
5. Oral Isotretinoin is prescription drug and the pharmacists should not dispense it as over the counter (OTC) drug.
6. This study consider as pilot study to assess the problem of oral Isotretinoin SE, specifically dryness and depression. Another study with different method of data collection is needed.

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