

Department of Clinical Sciences¹, Department of Pharmaceutical Sciences², College of Pharmacy and Health Sciences, Ajman University, Ajman, U.A.E.

Community pharmacist's' knowledge and practice toward oral isotretinoin prescription: a systemic review

Z. A. RASHID¹, M. M. AL-TABAKHA², M. J. ALOMAR¹

Received November 17, 2019, accepted December 16, 2019

*Corresponding author: Moawia Al-Tabakha, College of Pharmacy and Health Sciences, Ajman University, Ajman Al Jurf Area, United Arab Emirates
m.altabakha@ajman.ac.ae

Pharmazie 75: 56-60 (2020)

doi: 10.1691/ph.2020.9891

Background: Although oral isotretinoin capsules are widely dispensed in pharmacies due to their effectiveness in clearing acne, the legal, ethical and practice responsibilities of community pharmacist regarding this medicine have not been well evaluated. This systematic review of community pharmacist's role and professional practice toward oral isotretinoin is significant to help pharmacy regulators and educator's making decisions to improve therapy outcomes. **Review methods:** Eligible studies covering the period between 2009 and 2019 were identified by searching: Cochrane, PubMed and Google Scholar databases. **Results:** A total of 56 studies were reviewed. It showed that pharmacy professionals exhibited a very low level of medication knowledge and an unsatisfactory level of practice regarding isotretinoin. Most studies showed that women of childbearing age were unnecessarily exposed to isotretinoin. These results indicate poor compliance of community pharmacists with risk minimization programs such as pregnancy prevention program (PPP) in Europe and iPLEDGE in USA. **Conclusion:** Community pharmacists need additional education, training and awareness in the area of oral isotretinoin to evaluate its use and patient's eligibility especially for female patients of childbearing age. This review results are critical to pharmacy educators worldwide who are concerned in implementing and developing professional practice standards for community pharmacists regarding oral isotretinoin.

1. Introduction

Isotretinoin is a natural derivative of vitamin A. It is classified as prescription only medicine (POM). The first approval for severe acne treatment was in 1982 by Food and Drug administration (FDA). From 1982 to 2000, around 19.8 million of isotretinoin prescriptions were dispensed (Wysowski et al. 2002; FDA 2018). Numerous studies identified isotretinoin as the most clinically effective therapy for the condition (Kaymak and İler 2006; Layton 2009). Use of the drug leads to significant improvement with long term remission for many severe cases (Layton 2009). Unfortunately, the drug has been associated with several adverse effects including dryness of skin, lips, eyes, nose, teratogenicity, hyperlipidemia, pancreatitis, leukopenia, thrombocytopenia and transaminitis (Lee et al. 2016). There is a gap between the proven efficacy of isotretinoin capsules in clinic trials and their actual effectiveness in practice (Younis and Al-Harbi 2018). The reasons for this gap could be improper administration of the medicine, lack of adherence by patients to the prescribed treatment and medicine–medicine/ medicine–food interactions. As health-care professionals, pharmacists play an important role in improving access to health care and in filling the gap between the optimum efficacy of medicines and the actual value received. They have an important role in each part of a comprehensive health system (FIP 2013). For example, the pharmacists in USA and Australia were ranked as the second most ethical, trustworthy and honest professionals by 67% and 84% of the surveyed people, respectively (Kimmorley 2015; Marotta 2018). In view of this, the purpose of this review article is to systematically identify and analyze the available published articles about the community pharmacist's role toward oral isotretinoin prescription.

2. Investigations, results and discussion

2.1. Literature review

Eligible studies for review covered the period 2009-2019. The following databases were used: Cochrane, PubMed and Google Scholar. Cochrane includes 53 review groups to organize medical research findings that facilitate evidence based choices about health intervention. PubMed covers more than 28 million citations for life sciences and biomedical literature from MEDLINE and online books. Google Scholar includes online reviewed journals and books, conference, theses and other scholarly literature from diverse disciplines. Keywords used were: “pharmacists”, “pharmaceutical care”, “impact of pharmacist counseling”, “isotretinoin”, “isotretinoin SE” and “isotretinoin counseling by community pharmacist”. Each database used in this systematic review gives options for searching and filtration of the results. Advanced search was used to include articles in English language and the specific search terms had to be in the title. Those studies were additionally screened to identify those of relevance to this systematic review.

2.2. Description of included studies

Fifty six studies were included in the review after excluding all other irrelevant studies. Eight articles were excluded because they assessed the attitude and practice of health care professionals in general rather than focusing on pharmacists. Another five published articles assessing clinical pharmacist attitude in hospitals were also excluded. Furthermore, four studies were excluded because they evaluated community pharmacist counseling regarding diseases other than acne treated by isotretinoin such as rosacea, psoriasis

and skin cancers. The flow chart of the systematic review is shown in the Fig.

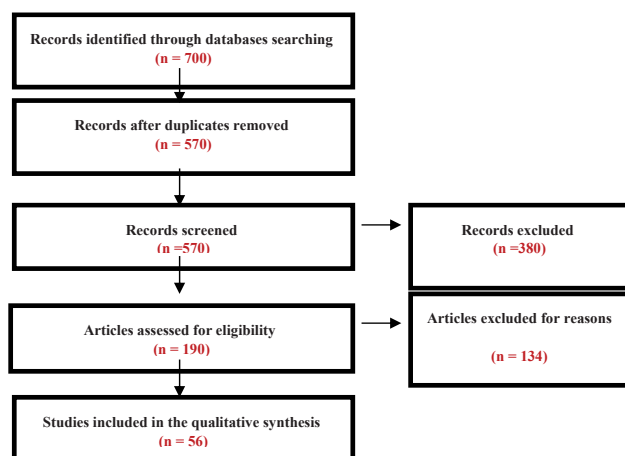


Fig.: Study flow chart showing the results of from searching databases.

2.3. Pharmacist interventions

2.3.1. Impact on professional collaboration

Pharmacists play a significant role among health care system professionals. Proper pharmacist's intervention leads to safe and effective use of medication to maximize therapeutic outcomes (Mobark et al. 2019). A study from North Carolina recognized the potential effectiveness of pharmaceutical services resulting from professional collaboration. At least 90% of physicians realized the positive effect of pharmacist contribution with adverse drug reactions management, prevention of drug-interactions/contraindications, medicines counseling and improving patient's compliance with the prescribed medicines. Around 74% of them reported the improvement of quality outcomes by community pharmacists (Pezzino et al. 2017). The impact of pharmacist's intervention was investigated in cases of inappropriate prescriptions such as: medication without indication, therapeutic duplication, inappropriate choice/use of medication, actual drug/food-interactions/contraindication and no medication prescribed for the diagnosed condition. In these cases, pharmacists communicated with the prescribers. As a result of this, the number decreased from 1845 to 238 (12.6% to 1.22%) during the period 2011-2016. Medication prescribed with no medical indication was the most inappropriate type identified by the pharmacists that was decreased annually after the intervention. Other types of errors were gradually eliminated by the end of 2016 (Bao et al. 2018).

2.3.2. Impact on drug related problems

Participation and intervention of community pharmacists have a positive influence in reducing drug related problems (DRPs) that contribute to morbidity and mortality. An interventional study was conducted to investigate the pharmacist potential in reducing DRPs in elderly patients who used six or more medicines (Vinks et al. 2009). Significant reduction was observed on the mean number of each patient DRPs after four months of intervention (mean difference 16.3%). They assumed that pharmacist effect will differ according to the nature of DRPs. It was more challenging to reduce DRPs if the cause was pharmacodynamic, pharmacokinetic or pharmaceutical. While in case of ADRs that related to patients or physicians attitude, behavior and level of knowledge it's easier to be influenced by pharmacist intervention. Pharmacist counseling improves medication adherence that minimizes adverse drug reactions (Leguelinel-Blache et al. 2015). This was investigated in 1844 patients through observational and interventional periods. The number of patients adherent to treatment regimen increased from 51 to 66.7% ($p < 0.01$). The percent of unfilled medications decreased from 50 to 32.5%. The impact of pharmacist counseling

on patients' drug-food interaction was evaluated in New York, USA (Volino et al. 2014). Participants were divided randomly into two groups. Patient medication monograph with counseling (PMMC) group experienced less incidence of food-drug interaction than patient medication monograph only (PMMO) group (22 versus 30%, respectively). About 70% of the participants realized the effectiveness of pharmacist counseling. The study highlighted that the main issues that affect patient's compliance were difficulties to remember the prescribed doses, incidence of food-drug interactions and inability to manage their medication regimen. In Croatia, the reported percent of patient's adherence increased slightly by only 3.5% when patients were interviewed at first and next visit. The reasons given for patients not asking questions about their disease/medication were worsening of patient's health state and negative side effects of the medicines. Moreover, pharmacist assumed that patients knew everything related to the dispensed medicines. This resulted in low chance of communication between pharmacist and patients which led the patients to be less interested on medication adherence (Boskovic et al. 2016).

2.3.3. Impact on patients' knowledge

Comprehensive pharmacist intervention was shown to improve patients' knowledge about their disease condition and medication therapy (Montgomery et al. 2010). In Ghana, positive results were reported according patients' knowledge about their medicines after been dispensed by the community pharmacists. The name, quantity and dosage of the prescribed medicines were mentioned clearly on the label in 98%, 99% and 55%, respectively. The corresponding percent of patient's knowledge were 63%, 80% and 75% respectively (Marfo et al. 2013). In contrast, patient's knowledge about medication safety was poor in Slovenia (Kos and Horvat 2015). They were familiar only with the normal basic information such as medication purpose, dose regimen and application rate. These results were attributed to the quality of pharmacist counseling that mainly focused on medications use instruction.

2.3.4. Barriers and errors associated with pharmacist intervention

Community pharmacists possess motivational attitude, behavior and positive intervention belief toward non-adherence intervention. Despite that, difficulties in follow-up and documentation with patients were mentioned as barriers for this intervention. In addition, some patients become defensive when the pharmacist counsels them about adherence (Witry 2018). In the US, an observational study found that direct encounter between pharmacist and their patients in addition to strict state regulations that require community pharmacists to counsel were found to be significant in improving therapeutic outcomes (Kimberlin et al. 2011). Norwegian pharmacists identified the significance of a pharmacy system that enhances the communication between pharmacist and their patients, utilization of technology and cooperation of pharmacist-patient or pharmacist-colleague at the pharmacy to solve medication problems (Mandt et al. 2010). Among 209 pharmacists in Australia, 82% realized an increase in dispensing errors. They justified these common errors by the huge number of dispensed medications, pharmacist exhaustion, confusing medicine names and misinterpretation of prescribers' hand writing. These obstacles must be overcome by implementing a systematic mechanism for checking the dispensing process, improving the medicines package, encourage typed prescription to be more obvious for the dispenser, minimize dispensing interruptions and ensures privacy during patients counseling (Peterson et al. 1999).

2.4. Isotretinoin

2.4.1. Efficacy

Numerous clinical trials proved the effectiveness of isotretinoin in treating severe cases of acne (Kaymak and İter 2006). Only 12.5% of patients developed a relapse that required another course

of isotretinoin treatment (Cyrulnik et al. 2012). In support of this, a retrospective study in Singapore demonstrated that the majority of patients (93.9%) developed complete remission or essential improvement since isotretinoin targets all the primary causes of acne (Gan et al. 2013). In contrast, one case of treatment failure in Sultan Qaboos hospital, in Oman was reported. However, this does not compromise isotretinoin's proven effectiveness (Al-Kathiri and Al-Najjar 2018). Isotretinoin reduces the incidence of scar formation with patients who had persistent acne (Chlebus and Chlebus 2019). On the other hand, it was reported that hypertrophic scars may developed during the treatment which may be related to inflammatory acne evolution (Guadanhim et al. 2016).

2.4.2. *Effective dose*

According British guidelines, isotretinoin is recommended in a dose of 1-2 mg/kg/day (BAD 2019). A randomized controlled trial was conducted to compare the efficacy of different dose regimen of isotretinoin. For severe cases they recommended high doses throughout the treatment period of isotretinoin (1 mg/kg/day) or using the high doses for the first eight weeks then maintenance with lower doses. For mild-moderate cases of acne, low doses (20 mg) gave effective and safe use (Agarwal et al. 2011). In Canada higher doses of isotretinoin are recommended due to their effectiveness on decreasing the chance of acne relapse (Blasiak et al. 2013). While, interestingly, for moderate-severe acne cases, it was found that disease severity decreased with only low doses (0.37 ± 0.11 mg/kg/day) of isotretinoin after 6-8 weeks of treatment (Van et al. 2019). Moreover, a low dose (5mg/day) of isotretinoin was highly effective in reducing the number of acne lesions in one randomized double blind study (Rademaker et al. 2014). It is unnecessary to overtreat mild/moderate cases with standard doses of isotretinoin, as the relapse rate and efficacy of low doses in mild/moderate cases were comparable with the standard dose (1 mg/kg/day) (Sardana and Garg 2010). As a comparative study in Korea suggested that low dose of isotretinoin is the best for patients suffering from moderate acne when the efficacy, tolerability and patient's satisfaction need to be considered (Lee et al. 2011).

2.4.3. *Safety concerns*

2.4.3.1 *Cutaneous adverse reactions*

Dry lip was the most commonly reported side effect that affects all isotretinoin patients (Brzezinski et al. 2017). This is followed by xerosis and facial erythema (95% and 66%, respectively). These were described as mild-well tolerated side effects and can be managed easily. In another retrospective study in 102 patients, it was found that 94% of patients suffered from dry lips and 72% from dry skin (Hodgkiss-Harlow et al. 2011). This is attributed to the mechanism of action of isotretinoin in reducing the severity of seborrhea which leads to stratum corneum dehydration and increase in the trans-epidermal water loss (Kmieć et al. 2013).

2.4.3.2. *Birth defects*

Despite the beneficial positive effect of isotretinoin in treating acne, its use is limited by the teratogenic adverse effect (Williams et al. 2012). The relationship between exposure and neonatal birth defects was investigated through a population-based cohort study. It was found that 9.4% of women gave birth to neonates with birth defects (Zomerdijk et al. 2014). In Germany 2010, 108 pregnancies were exposed to 20 mg of isotretinoin during the contraindicated period. 76% of pregnancies terminated because of the known medication risk. Five cases had spontaneous abortion. Within the 18 live births out of the 108 pregnancies, one case was observed with ventricular septal defect. They found that the chance of birth defect is much less in case of women exposed only during the first two weeks after conception than in women exposed beyond these periods (Schaefer et al. 2010). A prospective study of women using isotretinoin during the peri-conceptual periods showed that 11 women out of 56 suffered from spontaneous abortions and 44 women delivered normal healthy infants without any

birth defects even after the exposure to isotretinoin during the risk periods. But caution is still required as they used only low doses of isotretinoin and during the early period of pregnancy (Yook et al. 2012). The teratogenic property of isotretinoin was explained by the overexpression of the pro-apoptotic transcription factor (p53) that exacerbates apoptosis (Melnik 2018).

2.4.3.3. *Mental adverse reactions*

Significant exacerbation of mood symptoms is higher in patients with a previous history of mental disorders such as bipolar disease (Schaffer et al. 2010). Through reviewing the submitted reports to FDA from 1997 to 2017, no causal link was discovered, as the number of suicides among isotretinoin patients was lower than among general U.S populations. Other psychiatric side effects besides depression and suicide were reported but it was unclear if these side effects were related to isotretinoin therapy. As it was well established that patients with severe acne have a higher incidence of psychiatric afflictions because of their physical appearance (Metekoglu et al. 2019; Singer et al. 2019). Additionally, it was found that isotretinoin improves depression, patients anxiety, QOL and obsessive-compulsive symptoms associated with acne (Erdoğan et al. 2019).

2.4.3.4. *Effect on laboratory results*

According to the British Association of Dermatologists, isotretinoin can be associated with rare/reversible adverse events such as increase in the blood fat levels and mild liver inflammation (BAD 2019). Three randomized controlled trials were carried out to assess the laboratory values associated with isotretinoin use. Isotretinoin therapy resulted in a mild increase in serum cholesterol and triglycerides. In addition, there was a small rise in liver enzymes such as alanine transaminase (ALT) and aspartate aminotransferase (AST) (Nelson et al. 2009; Vieira et al. 2012; Ahmad 2015). It appears that the effect of isotretinoin on serum lipids was greater than the change in liver enzymes (Kızılyel et al. 2014). This is explained by the oral isotretinoin inducing apoptosis thereby reducing the expression of lipid metabolizing enzymes and the removal rate of the lipids from plasma (Nelson et al. 2009; Melnik 2017).

2.5. *Risk management programs*

To reduce or prevent adverse drug reactions associated with isotretinoin, risk management programs have been provided such as: pregnancy prevention program (PPP) in Europe and iPLEDGE in USA. It helps ensure that isotretinoin benefits outweigh the risks and ensures safety use by patients. Within these programs, isotretinoin must only be prescribed/dispensed by the physicians/pharmacists who were registered and activated in the program. The medicine will be dispensed only for patients who meet all the restrictions required by the respective program.

iPLEDGE is the latest and most strict risk minimization program mandated in USA by the FDA (iPLEDGE 2016). This program aims to inform prescribers, dispensers and patients about serious adverse drug reactions and safe-effective use instructions (FDA 2018). After applying iPLEDGE regulations, patient's access to isotretinoin therapy became more restricted by limiting the isotretinoin prescription from general practitioner to specialist providers (Kerr and Wosinska 2017). It emphasized the importance of concomitant use of contraceptives with isotretinoin due to the potential risk of birth defects while patients receiving the therapy. According to a pharmacy prescription claims-based study carried out in USA, it was found that the number of patients using contraceptives concomitantly with oral isotretinoin significantly increased after iPLEDGE implementation (P value = 0.02) (Pinheiro et al. 2013). Recently, it was shown that pregnancies, abortion and fetal birth defects were decreasing since the implementation of iPLEDGE program, because it improves female patient's access to effective long term and emergency contraceptive during the therapy (Tkachenko et al. 2019).

2.6. Pharmacist knowledge and practice toward isotretinoin

Six reviewed studies indicated that pharmacy professionals exhibited very low and unsatisfactory levels of medication knowledge and practice regarding isotretinoin. The absence of obligatory programs for pharmacist education and improving their counseling and dispensing skills is expected to have negative effects on the pharmaceutical care services that is provided by community pharmacists (Tuha et al. 2019). A study conducted in the Kingdom of Saudi Arabia (K.S.A.) showed that community pharmacists are not adequately aware about the potential risk of teratogenicity associated with isotretinoin use among female patients who lack the proper assessment for safe and eligible use of the medicine (Alrwisani et al. 2014). Surprisingly, only about half of the pharmacists (56%) knew the right pregnancy risk classification category (X), while the teratogenicity risk associated with oral isotretinoin was reported as the most serious effect by most of the pharmacists in the same study (78%). Only 6.2% of them advised the patients about using primary and secondary methods of contraception as recommended by the British guideline. Around 20% of the pharmacists were dispensing isotretinoin capsules without a prescription, while 11% of the participants did not check whether the patients undergo the required pregnancy tests before dispensing the isotretinoin capsules. Furthermore, among seventy-six pharmacists in Ethiopia, only twenty-six of them reported the contraindicated use of isotretinoin during pregnancy (Tuha et al. 2019). Unfortunately, pharmacist's recognition of isotretinoin drug-drug interactions is very poor. In a simulated patient study when ninety-seven pharmacists were asked for multivitamin supplement, only two pharmacist identified isotretinoin-vitamin A interaction by asking the patient about their medication history. On the other hand, when the pharmacists are informed about the simulated patients use of isotretinoin for severe acne, the number of pharmacists who recognized the interaction increased to fifteen out of the ninety-seven pharmacists (Dabaghzadeh and Hajjari 2018).

Continuous and up to date medication education for pharmacy professionals is required with multitude strategies that must be implemented to improve their skills in providing pharmaceutical care services. For example in India, when a structured continuous professional development program (CPD) was implemented to improve and update 48 community pharmacists skills and knowledge, a significant improvement ($p < 0.05$) was found in medication counseling (Adepu and Shariff 2010).

2.6.1. Compliance with iPLEDGE Program

According to the FDA, 40% of isotretinoin prescriptions that were prescribed through the system were denied due to the process. Multiple steps must be completed within restricted time to prescribe/dispense isotretinoin capsules which resulted in the interruption or discontinuation of the therapy course (Eichenfield and Krakowski 2015). Moreover, it was found that the strict regulations increased women's fear about teratogenic adverse effects but this did not translate to a significant reduction in pregnancy cases exposed to the risk (Kovitwanichkanont and Driscoll 2018). Consequently, around 150 female users of isotretinoin become pregnant each year despite their participation on the program. Because of a poor level of compliance with the system requirements to use two methods of contraceptives (primary and secondary) or female being abstinent from sexual intercourse (Collins et al. 2014). Community pharmacists demonstrated low level of adherence with the system requirements in a multicenter retrospective study (Cyrułnik et al. 2016). Analysis of conformity and contradiction between medical chart documentation and iPLEDGE data were carried out for patients who were treated with isotretinoin. The congruence was observed in 73% cases only. The contradiction was because isotretinoin was dispensed under the iPLEDGE program without corresponding medical chart documentation. A successful program must be implemented with simple regulations and provide patients with beneficial educational information about the effective use of contraceptives (Kovitwanichkanont and Driscoll 2018). The positive effect of providing female patients

with a contraceptive information sheet was proved (Werner et al. 2015). This is an effective additional way for improving patients' knowledge regarding the effective use of contraceptives during isotretinoin course of therapy.

An innovative system called "novel" program was implemented to help patients and providers to achieve treatment compliance. After 17 months of its implementation, 93% of the prescriptions had been filled successfully. These results demonstrate the significant improvement of isotretinoin treatment adherence that can be achieved by this system with fewer interruptions (Eichenfield and Krakowski 2015).

2.6.2. Pharmacist compliance with pregnancy prevention program (PPP)

Despite the implementation of pregnancy prevention programs in Europe, pregnant women were still exposed to isotretinoin therapy and some of them become pregnant within 30 days after the drug discontinuation. In the Netherlands about 60% of women started using isotretinoin while they were pregnant. This was attributed to the poor level of community pharmacist implementation of isotretinoin pregnancy prevention programs (Zomerdijk et al. 2014). One study reported that 82% of pharmacists checked on 30-days dispensing of isotretinoin and only half of them (53%) looked at the date of the prescription. Around 15% of patients were asked about a negative pregnancy test and 49% of the pharmacists checked whether the contraceptives were in use (Crijs et al. 2013). Furthermore, among women of reproductive age a cohort study was conducted. Within the study period, the use of isotretinoin increased and it was found that the concomitant use of hormonal contraceptives with isotretinoin therapy was only 59%. In addition, a high quantity of isotretinoin capsules was dispensed per each prescription that exceeds the allowed amount (Teichert et al. 2010). The issue of limited pharmacist implementation of PPP recommendations was manifested in France, as only 12% of women performed the pregnancy test and rarely repeated it during the treatment course (Raguideau et al. 2015). Recently, a study found that among 2797 women who received isotretinoin in Estonia, 15.7% were provided with full and 13.9% partial contraceptive coverage during the isotretinoin course in which pregnancy is contraindicated (Uusküla et al. 2018). Despite the stringent regulations of this program, the above results showed that patients' fear about the teratogenic risk increased rather than actually avoiding pregnancies exposure to isotretinoin (Kovitwanichkanont and Driscoll 2018). This failure in the implementation of the PPP must be investigated to identify the need for new measures such as through education or new set of regulations.

2.7. Conclusions

The results of this systematic review indicate that community pharmacists are not adequately aware about the potential risk associated with poor eligibility assessment, counseling and dispensing of oral isotretinoin capsules. It is evident from this results that community pharmacists need additional education and training in the area of oral isotretinoin. Emphasis should be laid on educating the pharmacists on how evaluate the use, efficacy and patient's eligibility to use the isotretinoin especially for female patients in childbearing age. This review results will be critical to pharmacy educators and regulators worldwide who are responsible in implementing and developing professional practice standards for community pharmacists regarding oral isotretinoin.

Conflict of interest: None declared.

References

- Adepu R, Shariff A (2010) Development, validation and implementation of continuous professional development programmes for community pharmacists. *Indian J Pharm Sci* 72: 557–563.
- Agarwal US, Besarwal RK, Bhola K (2011) Oral isotretinoin in different dose regimens for acne vulgaris: a randomized comparative trial. *Indian J Dermatol Venereol Leprol* 77: 688–694.

- Ahmad HM (2015) Analysis of clinical efficacy, side effects, and laboratory changes among patients with acne vulgaris receiving single versus twice daily dose of oral isotretinoin. *Dermatol Ther* 28: 151–157.
- Al-Kathiri L, Al-Najjar T (2018) Severe nodulocystic acne not responding to isotretinoin therapy successfully treated with oral dapson. *Oman Med J* 33: 433–436.
- Alrwisan AA, Alshammari TM, Tahir KW, Aleissa FM, Aljadhey HS (2014) Community pharmacists' knowledge of isotretinoin safety. *Saudi Med J* 35: 81–84.
- BAD (2019) British Association of Dermatologists - Patient Information Leaflets (PILs).
- Bao Z, Ji C, Hu J, Luo C, Fang W (2018) Clinical and economic impact of pharmacist interventions on sampled outpatient prescriptions in a Chinese teaching hospital. *BMC Health Serv Res* 18: 519.
- Blasiak RC, Stamey CR, Burkhart CN, Lugo-Somolinos A, Morrell DS (2013) High-dose isotretinoin treatment and the rate of retreat, relapse, and adverse effects in patients with acne vulgaris. *JAMA Dermatol* 149: 1392–1398.
- Boskovic J, Mestrovic A, Leppee M, Bago M, Sostar Z, Naletilic D (2016) Pharmacist competences and impact of pharmacist intervention on medication adherence: an observational study. *Psychiatr Danub* 28: 420–427.
- Brzezinski P, Borowska K, Chiriac A, Smigielski J (2017) Adverse effects of isotretinoin: A large, retrospective review. *Dermatol Ther* 30: e12483.
- Chlebus E, Chlebus M (2019) The role of adolescent acne treatment in formation of scars Among patients with persistent adult acne: evidence from an observational study. *Cutis* 104: 57–61.
- Collins M-K, Moreau JF, Opel D, Swan J, Prevost N, Hastings M, Schwarz EB, Ferris LK (2014) Compliance with pregnancy prevention measures during isotretinoin therapy. *J Am Acad Dermatol* 70: 55–59.
- Crijns I, Mantel-Teeuwisse A, Bloemberg R, Pinas E, Straus S, de Jong-van den Berg L (2013) Healthcare professional surveys to investigate the implementation of the isotretinoin Pregnancy Prevention Programme: a descriptive study. *Expert Opin Drug Saf* 12: 29–38.
- Cyrułnik AA, Gewirtzman AJ, Paz KB, Glick JB, Anam AK, Carrasco DA, Shalita AR, Cohen SR (2016) iPLEDGE Weaknesses: Is It Time to Address the Flaws? *J Drugs Dermatol* 15: 97–102.
- Cyrułnik AA, Viola KV, Gewirtzman AJ, Cohen SR (2012) High-dose isotretinoin in acne vulgaris: improved treatment outcomes and quality of life. *Int J Dermatol* 51: 1123–1130.
- Dabaghzadeh F, Hajjari R (2018) Practice of community pharmacists related to multivitamin supplements: a simulated patient study in Iran. *Int J Clin Pharm* 40: 190–195.
- Eichenfield LF, Krakowski AC (2015) A novel patient support program to address isotretinoin adherence: proof-of-concept analysis. *J Drugs Dermatol* 14: 375–379.
- Erdogan Y, Erturan İ, Aktepe E, Akyıldız A (2019) Comparison of quality of life, depression, anxiety, suicide, social anxiety and obsessive-compulsive symptoms between adolescents with acne receiving isotretinoin and antibiotics: a prospective, non-randomised, Open-Label Study. *Pediatr Drugs* 21: 195–202.
- FDA (2018) Isotretinoin (marketed as Accutane) Capsule Information.
- FIP (2013) Community Pharmacy Section.
- Gan EY, Koh W-P, Jin AZ, Tan AWH, Tan HH, Tang MBY (2013) Isotretinoin is safe and efficacious in Asians with acne vulgaris. *J Dermatol Treat* 24: 387–391.
- Guadanhim LRS, Gonçalves RG, Bagatin E (2016) Observational retrospective study evaluating the effects of oral isotretinoin in keloids and hypertrophic scars. *Int J Dermatol* 55: 1255–1258.
- Hodgkiss-Harlow CJ, Eichenfield LF, Dohil MA (2011) Effective monitoring of isotretinoin safety in a pediatric dermatology population: A novel "patient symptom survey" approach. *J Am Acad Dermatol* 65: 517–524.
- iPLEDGE (2016) SAFETY NOTICE.
- Kaymak Y, İler N (2006) The effectiveness of intermittent isotretinoin treatment in mild or moderate acne. *J Eur Acad Dermatol Venereol* 20: 1256–1260.
- Kerr KW, Wosinska ME (2017) Patient access in restrictive risk management programs: The case of iPLEDGE. *Ther Innov Regul Sci* 51:16–23.
- Kimberlin CL, Jamison AN, Linden S, Winterstein AG (2011) Patient counseling practices in U.S. pharmacies: effects of having pharmacists hand the medication to the patient and state regulations on pharmacist counseling. *J Am Pharm Assoc* 51: 527–534.
- Kimmerley S (2015) RANKED: Australia's 20 most trusted professions. *Bus Insid Aust*. Available at: <https://www.businessinsider.com.au/ranked-australias-20-most-trusted-professions-2015-5> Accessed September 30, 2019.
- Kızılyel O, Metin MS, Elmas ÖF, Çayır Y, Aktaş A (2014) Effects of oral isotretinoin on lipids and liver enzymes in acne patients. *Cutis* 94: 234–238.
- Kmieć ML, Pajor A, Broniarczyk-Dyla G (2013) Evaluation of biophysical skin parameters and assessment of hair growth in patients with acne treated with isotretinoin. *Adv Dermatol Allergol Dermatol Alergol* 30: 343–349.
- Kos M, Horvat N (2015) Contribution of Slovenian community pharmacist counseling to patients' knowledge about their prescription medicines: a cross-sectional study. *Croat Med J* 56: 41–49.
- Kovitwanichkanont T, Driscoll T (2018) A comparative review of the isotretinoin pregnancy risk management programs across four continents. *Int J Dermatol* 57: 1035–1046.
- Layton A (2009) The use of isotretinoin in acne. *Dermatoendocrinol* 1: 162–169.
- Lee JW, Yoo KH, Park KY, Han TY, Li K, Seo SJ, Hong CK (2011) Effectiveness of conventional, low-dose and intermittent oral isotretinoin in the treatment of acne: a randomized, controlled comparative study. *Br J Dermatol* 164:1369–1375.
- Lee YH, Scharnitz TP, Muscat J, Chen A, Gupta-Elera G, Kirby JS (2016) Laboratory monitoring during isotretinoin therapy for acne: a systematic review and meta-analysis. *JAMA Dermatol* 152: 35–44.
- Leguelinel-Blache G, Dubois F, Bouvet S, Roux-Marson C, Arnaud F, Castelli C, Ray V, Kinowski J-M, Sotto A (2015) Improving patient's primary medication adherence. *Medicine (Baltimore)* 94: e1805.
- Mandt I, Horn AM, Ekedahl A, Granas AG (2010) Community pharmacists' prescription intervention practices--exploring variations in practice in Norwegian pharmacies. *Res Soc Adm Pharm* 6: 6–17.
- Marfo AF, Owusu-Daaku FT, Kyerewaa-Akromah E (2013) Patient knowledge of medicines dispensed from Ghanaian community pharmacies. *Pharm Pract* 11: 66–70.
- Marotta R (2018) Pharmacists Remain Among Most Trusted and Ethical Professionals. *Pharm Times*. Available at: <https://www.pharmacytimes.com/news/pharmacists-remain-among-most-trusted-and-ethical-professionals> Accessed November 3, 2019.
- Melnik BC (2018) Overexpression of p53 explains isotretinoin's teratogenicity. *Exp Dermatol* 27: 91–93.
- Melnik BC (2017) Apoptosis may explain the pharmacological mode of action and adverse effects of isotretinoin, including teratogenicity. *Acta Derm Venereol* 97: 173–181.
- Metekoglu S, Oral E, Ucar C, Akalin M (2019) Does isotretinoin cause depression and anxiety in acne patients? *Dermatol Ther* 32: e12795.
- Mobark DM, Al-Tabakha MM, Hasan S (2019) Assessing hormonal contraceptive dispensing and counseling provided by community pharmacists in the United Arab Emirates: a simulated patient study. *Pharm Pract* 17: 1465.
- Montgomery AT, Kettis Lindblad Å, Eddyby P, Söderlund E, Tully MP, Källemark Spörng S (2010) Counselling behaviour and content in a pharmaceutical care service in Swedish community pharmacies. *Pharm World Sci* 32: 455–463.
- Nelson AM, Zhao W, Gilliland KL, Zaenglein AL, Liu W, Thiboutot DM (2009) Temporal changes in gene expression in the skin of patients treated with isotretinoin provide insight into its mechanism of action. *Dermatoendocrinol* 1: 177–187.
- Peterson GM, Wu MS, Bergin JK (1999) Pharmacist's attitudes towards dispensing errors: their causes and prevention. *J Clin Pharm Ther* 24: 57–71.
- Pezzino NC, Marciniak MW, Smith MG, Ferreri SP (2017) Physician-reported factors that encourage collaboration with community pharmacists. *J Am Pharm Assoc, Residency Issue* 57: S279-S283.e2.
- Pinheiro SP, Kang EM, Kim CY, Governale LA, Zhou EH, Hammad TA (2013) Concomitant use of isotretinoin and contraceptives before and after iPLEDGE in the United States. *Pharmacoepidemiol Drug Saf* 22: 1251–1257.
- Rademaker M, Wishart JM, Birchall NM (2014) Isotretinoin 5 mg daily for low-grade adult acne vulgaris--a placebo-controlled, randomized double-blind study. *J Eur Acad Dermatol Venereol* 28:747–754.
- Raguideau F, Mezzarobba M, Zureik M, Weill A, Ricordeau P, Alla F (2015) Compliance with pregnancy prevention plan recommendations in 8672 French women of child-bearing potential exposed to acitretin. *Pharmacoepidemiol Drug Saf* 24: 526–533.
- Sardana K, Garg VK (2010) Efficacy of low-dose isotretinoin in acne vulgaris. *Indian J Dermatol Venereol Leprol* 76: 7–13.
- Schaefer C, Meister R, Weber-Schoendorfer C (2010) Isotretinoin exposure and pregnancy outcome: an observational study of the Berlin Institute for Clinical Teratology and Drug Risk Assessment in Pregnancy. *Arch Gynecol Obstet* 281: 221–227.
- Schaffer LC, Schaffer CB, Hunter S, Miller A (2010) Psychiatric reactions to isotretinoin in patients with bipolar disorder. *J Affect Disord* 122: 306–308.
- Singer S, Tkachenko E, Sharma P, Barbieri JS, Mostaghimi A (2019) Psychiatric adverse events in patients taking isotretinoin as reported in a food and drug administration database from 1997 to 2017. *JAMA Dermatol* 155: 1162–1166.
- Teichert M, Visser LE, Dufour M, Rodenburg E, Straus SM, Smet PA, Stricker BHC (2010) Isotretinoin use and compliance with the Dutch Pregnancy Prevention Programme. *Drug Saf* 33: 315–326.
- Tkachenko E, Singer S, Sharma P, Barbieri J, Mostaghimi A (2019) US Food and Drug Administration reports of pregnancy and pregnancy-related adverse events associated with isotretinoin. *JAMA Dermatol* 155: 1175–1179.
- Tuha A, Gurbie Y, Hailu HG (2019) Evaluation of knowledge and practice of pharmacy professionals regarding the risk of medication use during pregnancy in Dessie town, Northeast Ethiopia: a cross-sectional study. *J Pregnancy* 2019: 2186841.
- Uusküla A, Pisarev H, Kurvits K, Laius O, Laanpere M, Uusküla M (2018) Compliance with pregnancy prevention recommendations for isotretinoin in Estonia in 2012–2016. *Drugs - Real World Outcomes* 5: 129–136.
- Van TLT, Minh PN, Thuy PTT, Gandolfi M, Satolli F, Feliciani C, Tirant M, Vojvodic A, Lotti T (2019) Efficacy of oral low-dose isotretinoin in the treatment of Acne vulgaris in Vietnam. *Open Access Maced J Med Sci* 7: 279–282.
- Vieira AS, Beijamini V, Melchioris AC (2012) The effect of isotretinoin on triglycerides and liver aminotransferases. *An Bras Dermatol* 87: 382–387.
- Vinks THAM, Egberts TCG, de Lange TM, de Koning FHP (2009) Pharmacist-based medication review reduces potential drug-related problems in the elderly: the SMOG controlled trial. *Drugs Aging* 26: 123–133.
- Volino LR, Das RP, Mansukhani RP, Cosler LE (2014) Evaluating the potential impact of pharmacist counseling on medication adherence using a simulation activity. *Am J Pharm Educ* 78: 169.
- Werner CA, Papic MJ, Ferris LK, Schwarz EB (2015) Promoting safe use of isotretinoin by increasing contraceptive knowledge. *JAMA Dermatol* 151: 389–393.
- Williams HC, Dellavalle RP, Garner S (2012) Acne vulgaris. *Lancet* 379: 361–372.
- Witry MJ (2018) Medication adherence beliefs of US community pharmacists. *Res Soc Adm Pharm* 14: 471–478.
- Wysowski DK, Swann J, Vega A (2002) Use of isotretinoin (Accutane) in the United States: rapid increase from 1992 through 2000. *J Am Acad Dermatol* 46: 505–509.
- Yook J-H, Han J-Y, Choi J-S, Ahn H-K, Lee S-W, Kim M-Y, Ryu H-M, Nava-Ocampo AA (2012) Pregnancy outcomes and factors associated with voluntary pregnancy termination in women who had been treated for acne with isotretinoin. *Clin Toxicol* 50: 896–901.
- Younis NS, Al-Harbi NY (2018) Public understanding and awareness of isotretinoin use and safety in Al Ahsa, Eastern Saudi Arabia. *Ther Innov Regul Sci* 2168479018807677.
- Zomerdijk IM, Ruiters R, Houweling LM, Herings RM, Sturkenboom MC, Straus SM, Stricker BH (2014) Isotretinoin exposure during pregnancy: a population-based study in The Netherlands. *BMJ Open* 4: e005602.