Pharmacoepidemiology and Drug Safety

WILEY

ORIGINAL ARTICLE OPEN ACCESS

The Awareness of and Adherence to the Pregnancy Prevention Program for Oral Retinoids: A Questionnaire Survey in Denmark

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Received: 15 March 2024 | **Revised:** 29 August 2024 | **Accepted:** 16 September 2024

Funding: The authors received no specific funding for this work.

Keywords: Denmark | healthcare professionals | oral retinoids | patients | pharmacists | pregnancy prevention | questionnaires

ABSTRACT

Purpose: We aimed to investigate the awareness of oral retinoid teratogenicity and the adherence to the pregnancy prevention program (PPP) related to oral retinoid use by physicians, pharmacists, and patients in Denmark.

Methods: As part of the multi-country survey, web-based questionnaires were distributed among Danish dermatologists, general practitioners, community pharmacists, and women of childbearing age, who were using or had used oral retinoids within the past 5 years.

Results: A total of 62 physicians, 96 pharmacists, and 50 oral retinoid using women responded; 95%, 100%, and 98%, respectively, were aware of the teratogenic risks of oral retinoids. For physicians, the most applied PPP measures were the usage of the patient (44%) and the healthcare professional (19%) guides, while the least applied measure was signing medication risk awareness form (3%). Among the pharmacists, the warning sign on the outer medication package was the most used measure (45%). Among the women, a majority (90%) had read the patient information leaflet included in the medication package and 72% discussed the use of contraception with their healthcare provider, while risk awareness forms and patient cards were seen by only few.

Conclusions: In Denmark, physicians, pharmacists, and medicine users were aware about the teratogenic effects of oral retinoids. Adherence to pregnancy prevention measures varied, suggesting unwillingness to use the measures that require patients' signatures among physicians and a lack of awareness of pharmacy targeting measures. Accessibility of the latter measures need to be optimized to improve the safety of oral retinoid use.

1 | Introduction

Oral retinoids, such as acitretin, alitretinoin, and isotretinoin, belong to a class of medications derived from vitamin A. They work by regulating cell growth and differentiation and are commonly prescribed to address severe skin conditions such as acne, psoriasis, and specific forms of skin cancer [1]. Despite their therapeutic benefits, oral retinoids come with a notable caveat—their association with teratogenic effects during pregnancy, or the potential to cause birth defects in the developing fetus when exposed to the drug in utero [2].

Several case reports and observational studies, emerging just a few years after the introduction of isotretinoin in Europe in

Summary

- We aimed to investigate the awareness of oral retinoid teratogenicity and adherence to the pregnancy prevention program (PPP) among oral retinoid prescribers, dispensers, and users.
- Web-based questionnaires were distributed to Danish dermatologists, general practitioners, community pharmacists, and women of childbearing age who had used oral retinoids within the past 5 years.
- A high percentage of respondents were aware of oral retinoids teratogenicity, but adherence to PPP measures, such as patient guides, healthcare professional guides, risk awareness forms, varied.
- Feasibility and accessibility of certain PPP measures need to be optimized to enhance the safety of oral retinoid use in the country.

1984, have documented the effects of oral retinoids on miscarriages and congenital structural anomalies, including those affecting the central nervous system (CNS) and leading to subsequent psychomotor and intellectual retardation [3–5]. Because of these effects, the European Medicines Agency (EMA) recommended restricting their use in pregnant or potentially pregnant women as early as 2003, but despite these recommendations, there has still been a high exposure to oral retinoids among women of childbearing age [6, 7]. Therefore, in 2018 The EMA Pharmacovigilance Risk Assessment Committee (PRAC) updated the recommendations on oral retinoid use in pregnant or potentially pregnant women [8], stating that the use of oral retinoids is contraindicated in reproductive-age women without following a Pregnancy Prevention Program (PPP). The PPP outlines oral retinoid use safety measures for the women and their healthcare professionals (HCPs), including pregnancy testing before, during, and after treatment, contraception use throughout treatment, switching to alternative medication before conception, and reviewing and signing a Risk Acknowledgment Form (RAF). Educational materials, such as patient, HCP and pharmacist guides, patient reminder cards with appointment dates, direct HCP communication letters (DHCP), and visual warnings on medication packaging aim to enhance awareness and adherence to these safety measures [9].

Research focusing on the awareness of and adherence to the PPP related to oral retinoid use is sparse. Most of the publications originate from North America, while information specific for the European situation is limited [10, 11]. Hence, in 2019, the EMA initiated a multi-country survey across eight European countries (Belgium, Denmark, Greece, Latvia, Portugal, The Netherlands, Slovenia, and Spain) to gather information on when and where HCPs and patients became aware of the teratogenicity of oral retinoids. The survey also assessed adherence to and the impact of the updated pregnancy prevention recommendations regarding the prescription, dispensing, and use of oral retinoids. The aim of this study is to describe pregnancy prevention practices by physicians, pharmacists, and patients in the processes of prescribing, dispensing, and using oral retinoids in Denmark.

2 | Methods

2.1 | Development of the Questionnaires

A panel of experts consisting of social and clinical pharmacy researchers from the eight European countries developed three questionnaires: for dermatologists and general practitioners (GPs), for pharmacists, and for patients who either use or have used oral retinoids. The questionnaires for physicians and pharmacists inquired about their awareness of the teratogenic effects of oral retinoids and their knowledge of and adherence to the PPP. The patient questionnaire contained queries about their knowledge and experience with the PPP, including pregnancy testing (prior to, during, and after treatment initiation) and the use of effective contraception throughout the treatment. The questionnaires were developed and pilot-tested in English. The Danish team pilot tested the questionnaires by interviewing patients, medical specialists, and pharmacists who had experience taking, prescribing or dispensing oral retinoids. The piloting of the questionnaires with GPs took place in the Netherlands. Subsequently, the questionnaires were translated into national languages following a prepared protocol. For this study, the questionnaires were translated into Danish. The finalized questionnaires were transferred to the online survey system Lime.

2.2 | Recruitment

Participants were recruited between January 2019 and September 2020 using convenience sampling. Questionnaire links were shared in digital newsletters of selected professional and patients' organizations, and Facebook groups: the Danish Society for General Practitioners, Danish Dermatologists' Society, Danish Pharmacists Association, Network for the Development of Pharmacy Practice in Denmark, Facebook groups Isotretinoin Danish/Swedish/Norwegian, acne-forum, and acne and pimples. Doctors and pharmacists who had never prescribed, consulted on, or dispensed an oral retinoid were excluded. Patients were included if they were female, born between 1969 and 2004 (i.e., aged 15–50 years old during the study), not pregnant, and currently or previously using oral retinoids. Pregnant women were excluded due to the potential lack of awareness of the risks associated with oral retinoids. These women were encouraged to consult their GP or medical specialist to ensure the safe use of their medication. The respondents were not reimbursed or compensated for time to complete the survey.

2.3 | Analysis

Descriptive data analyses, reporting frequencies and percentages, were conducted using SPSS Statistics version 27. Differences between the responses to the physicians' questionnaire between GPs and dermatologists were analyzed using Chi-square tests.

2.4 | Consent

All respondents were informed about the study aims and provided informed consent before responding to the questionnaire.

3 | Results

3.1 | Physicians

A total of 80 individuals initiated the online questionnaire, and after exclusions, 62 physicians were included. Reasons for exclusion were not being a physician and failure to provide informed consent (Figure S1). The mean age was 50 years old, and 53% were female. Just over half were dermatologists. Dermatologists claimed encountering reproductive age women using oral retinoids more often than GPs (Table 1).

Nearly all physicians (95%, $n = 59$) were aware of the teratogenic effects of oral retinoids; two individuals who did not know about it and became aware via the survey were GPs; 81% ($n = 50$)—more dermatologists than GPs—had learned about these effects more than 5 years ago (Table S1). The majority (59%, $n = 35$) obtained this information during their academic education. Dermatologists more often than GPs mentioned professional societies, symposia/conferences, and manufacturers as their sources of information (Table S2). Among the PPP measures, the patient guide was reported as the most used measure (used by 50%), followed by the HCP guide (used by 22%). More dermatologists than GPs reported using both the patient and HCP guides. Additionally, more GPs than dermatologists claimed that they would not use the patient guide in the future. The measures reported as the least used and most unlikely to be used in the future—with no differences between dermatologists and GPs—were signing (2% and 3%, respectively) and reviewing (6% and 4%, respectively) the RAF (Table 2).

The reported oral retinoid prescribing and related pregnancy prevention practices among all responding physicians are outlined in Table 3. All dermatologists claimed to discontinue the prescription for women who became pregnant, as well as conducting pregnancy testing before initiating and during oral retinoid treatments, while the vast majority of GPs claimed to prescribe oral contraceptives (Table S1).

Finally, 72% ($N = 38$) of the physicians stated that their prescribing and counseling practices for women of reproductive age taking oral retinoids did not change, and only three (6%) stated that it did change since the implementation of the PPP for oral retinoids in 2018 (Table S3). Out of these three, two thought that the patient guide had the most impact (Table S4).

3.2 | Pharmacists

A total of 127 individuals started the online questionnaire, and after exclusions, 96 pharmacists were included. Reasons for exclusion were not obtaining informed consent, not answering any questions, not being a pharmacist, and never having dispensed oral retinoids (Figure S2). The mean age of the included pharmacists was 38 years, 75% were female. All worked in a community pharmacy, a bit more than half had practiced in their current profession for 0–5 years. The majority dispensed oral retinoids

TABLE 1 | Characteristics of physicians, $N = 62$.

Characteristics		*N* (%) unless otherwise indicated
Age	Mean (SD)	49.6 (10.19)
	Median (IQR)	48.5 (43–57)
	Range	30–71
Gender, *N* (%)	Female	33 (53.2%)
	Male	27 (43.5%)
	Rather not say	2 (3.2%)
Professional category, *N* (%)	Dermatologist	33 (53.2%)
	General practitioner	25 (40.3%)
	Other	4 (6.5%)
Period of time practicing current profession, *N* (%)	0–5 years	18 (29.0%)
	6–10 years	10 (16.1%)
	11–20 years	19 (30.6%)
	Over 20 years	15 (24.2%)
Frequency of consulting women of reproductive age who are taking oral retinoids, *N* (%)*	Once a week or more	34 (54.8%)
	2–3 times a month	6 (9.7%)
	Once a month or less	22 (35.5%)

*significant differences between GPs and dermatologists, with more dermatologists than GPs seeing patients once a week or more (91% vs. 12%, respectively), and less dermatologists than GPs seeing patients once a month or less (9% vs. 68%, respectively), $p < 0.001$.

TABLE 2 | The use of education materials from the PPP by physicians, *N* (%), *N* total = 54.

Use of educational materials	HCP guide*	Patient guide*	Review RAF	Signing RAF	Patient reminder card	DHPC
Yes	12 (22.2%)	27 (50.0%)	6 (11.1%)	2 (3.7%)	9 (16.7%)	9 (16.7%)
Not sure/no	42 (77.8%)	27 (50.0%)	48 (88.9%)	52 (96.3%)	45 (83.3%)	45 (83.3%)
If no, likely to use in the future	11 (20.4%)	10 (18.5%)	4 (7.5%)	3 (5.6%)	10 (18.5%)	8 (14.8%)
If no, unlikely to use in the future	22 (40.7%)	12 (22.2%)	30 (55.6%)	35 (64.8%)	25 (46.3%)	27 (50.0%)

Abbreviations: DHPC = direct healthcare communication, HCP = health care professional, RAF = risk acknowledgment form.
*Significant differences between dermatologists and GPs, with more dermatologist than GPs using the HCP guide: 23.3%. vs. 15.0% ($p = 0.003$), and the patient guide: 76.7% vs. 10.0% ($p < 0.001$), and more GPs than dermatologist having no intentions to use the patient guide in the future: 55.0% vs. 3.3% ($p = 0.003$).

and provided information about oral retinoids to women of reproductive age a few times a month (Table 4).

All pharmacists were aware of the teratogenicity of oral retinoids; 63% ($n = 60$) got aware about it more than 5 years ago (Table S6). Academic studies (58%, $n = 56$) and manufacturers (48%, $n = 46$) were the most often mentioned sources for obtaining this information (Table S7). From the PPP measures, the use of the warning sign on the outer medication package was distinctly the most often applied, while the patient reminder card was the least often applied PPP both currently and for future encounters (Table 5).

While dispensing oral retinoids, pharmacists most often provided information about the importance of effective contraception (79%) and least often advised patients to stop taking their medication in case of pregnancy (59%) (Table 6).

The majority of pharmacists (68%, $n = 46$) claimed that the information they provided to women of reproductive age when dispensing oral retinoids did not change since the implementation of the PPP in 2018 (Table S8). For the 18% ($n = 14$), who reported a change in their dispensing practice, the warning sign on the outer packaging had the highest impact (Table S9).

3.3 | Patients

A total of 74 individuals initiated the online questionnaire, and after exclusions, 50 patients were included. Reasons for exclusion were not providing informed consent, not meeting gender and age criteria, and either not answering any questions or only answering the demographic questions (Figure S3). The mean age of patients was 26 years, the most common levels of education were secondary school and university (42% each). The respondents reported that the most frequently used oral retinoids were isotretinoin or accutane: 72% claimed currently using it, and 28% stated that they had used it earlier (Table 7).

All but one was aware of the teratogenic effects of oral retinoids (Table S10). The majority obtained the information from their dermatologist (71%, $n = 35$) and the patient information leaflet (PIL) (65%, $n = 32$) (Table S11). Concerning the PPP, the largest proportion (90%, $n = 45$) had read the PIL included in the medication package; about half saw the warning sign on the outer packaging and were tested for pregnancy before and during the treatment. Only a few reported receiving a patient reminder card with appointments or reviewing and signing the RAF (Table 8).

For most patients, the use of oral retinoids did not appear to change since the implementation of the PPP in 2018: 38% ($n = 18$) stated that they used oral retinoids in the same way as before 2018, while 34% ($n = 16$) were unsure if there had been any change (Table S12).

4 | Discussion

This study assessed the awareness of and adherence to the measures from the PPP related to the use of oral retinoids among

TABLE 3 | Physicians' practices when prescribing oral retinoids to women of reproductive age, $N = 52$.

Prescribing habits	Agree, *N* (%)	Disagree, *N* (%)	Not relevant, *N* (%)
No prescription to women of reproductive age	16 (30.8%)	30 (57.7%)	6 (11.5%)
Careful when prescribing to women of reproductive age	33 (63.5%)	5 (9.6%)	14 (26.9%)
Stop oral retinoid treatment in case of a pregnancy	47 (90.4%)	0 (0.0%)	5 (9.6%)
Refer to a medical specialist when suspect a pregnancy	25 (48.1%)	7 (13.5%)	20 (38.5%)
Pregnancy testing			
Before starting treatment	39 (75.0%)	0 (0.0%)	13 (25.0%)
Monthly during treatment	36 (69.2%)	2 (3.8%)	14 (26.9%)
After stopping treatment	34 (65.4%)	4 (7.7%)	14 (26.9%)
Discuss the results	33 (63.5%)	4 (7.7%)	15 (28.8%)
Effective contraception			
Discuss	37 (71.2%)	1 (1.9%)	14 (26.9%)
Prescribe	26 (50.0%)	19 (36.5%)	7 (13.5%)
Refer to a GP or a medical specialist	33 (63.5%)	2 (3.8%)	17 (32.7%)

Danish physicians, pharmacists, and patients. It revealed a high awareness of the teratogenic risks associated with oral retinoids, but the adherence to and the impact of the pregnancy prevention measures during the prescription, dispensing, and use of oral retinoids was not extensive.

Interestingly, Danish pharmacists demonstrated a higher awareness of oral retinoid teratogenicity compared to physicians: three physicians (none of them dermatologists), in contrast to no pharmacists, did not know that oral retinoids are teratogenic before answering the questionnaire. Additionally, pharmacists had acquired knowledge about the teratogenicity of oral retinoids more recently than physicians, which possibly was influenced by the age difference: in the study, pharmacists had a mean age of 37.9 years, while physicians averaged 49.6 years. When comparing the findings of the study in Denmark with the averages from the multinational European study, the awareness among Danish pharmacists was slightly higher (100% vs. 96% in Denmark vs. Europe) and the awareness among Danish physicians was almost equal (96% vs. 97% in Denmark vs. Europe) [12]. Notably, the situation with awareness of the teratogenicity of valproate in the previously conducted similar studies was reversed: Danish pharmacists were less aware than both Danish physicians and their European colleagues about the teratogenicity of valproate [12, 13]. Such a situation reveals the need for better education on the teratogenicity of oral retinoids among Danish physicians, particularly GPs, who in Denmark do not prescribe oral retinoids but are involved in advising women on pregnancy prevention. In terms of patient awareness, knowledge regarding the teratogenicity of oral retinoids was slightly higher in Denmark compared to the European average: 98% vs. 96%, respectively [12]. Additionally, awareness about the teratogenicity of oral retinoids was considerably higher than the awareness of the teratogenicity of valproate, as reported in the previously conducted study: 98% vs. 82% for retinoids vs. valproate, respectively [13]. This may be influenced by the fact that oral retinoids are more teratogenic than valproate, and the fact that the evidence regarding the teratogenicity of oral retinoids was confirmed by regulatory agencies earlier than for valproate: in 2003 compared to 2014 [14, 15].

Similar to the previously conducted study on valproate [13], this study revealed that adherence to and impact of pregnancy prevention measures when prescribing, dispensing, and using of oral retinoids was not extensive. Among Danish physicians, the signing and reviewing the RAF with patients using oral retinoids, mirroring the situation with valproate users [13], emerged as the least utilized measures within the PPP: 11.1% vs. 3.7% of physicians reported reviewing and signing the RAF with oral retinoid users, respectively. Reviewing and signing the RAF were also considered as the measures, which were the least likely to be employed in the future. Furthermore, the percentages of physicians reporting reviewing and signing the RAF with patients using oral retinoids in Denmark were considerably lower than in other European countries: the average percentages of physicians who claimed reviewing and signing the RAF for oral retinoids in the European study were 40% and 34%, respectively [12]. The given situation might be indicative of specific cultural aspects within the Danish healthcare system. In Denmark, the emphasis is placed on cultivating a relationship between patients and physicians based on trust rather than formalities. Indeed, in a cross-country study comparing trust in physicians, Denmark was ranked among the countries

TABLE 4 | Characteristics of the pharmacists, $N = 96$.

Characteristics		*N* (%) unless otherwise indicated
Age	Mean (SD)	37.9 (11.38)
	Median (IQR)	34.00 (29–45)
	Range	26–68
Gender, *N* (%)	Female	72 (75.0%)
	Male	24 (25.0%)
	Rather not say	0 (0.0%)
Professional category, *N* (%)	Community pharmacist	96 (100.0%)
	Hospital pharmacist	0 (0.0%)
Period of time practicing current profession, *N* (%)	0–5 years	49 (51.0%)
	6–10 years	14 (14.6%)
	11–20 years	21 (21.9%)
	Over 20 years	12 (12.5%)
Frequency of dispensing oral retinoids for women of reproductive age, *N* (%)	Once a week or more	23 (24.0%)
	A few times a month	52 (54.2%)
	Once a month or less frequently	21 (21.9%)
Frequency of providing information to women of reproductive age about oral retinoids, *N* (%)	Once a week or more	20 (20.8%)
	A few times a month	44 (45.8%)
	Once a month or less frequently	31 (32.3%)
	Never	1 (1.0%)

with high levels of trust in HCPs [16]. To substantiate the claim regarding the professionalism of Danish physicians when prescribing oral retinoids to women of reproductive age, this study showed that every prescriber reported ceasing administration of oral retinoids to pregnant women. Additionally, all dermatologists claimed to conduct pregnancy tests before initiating and during the treatment.

The situation is not as positive concerning pharmacists not utilizing a checklist designed specifically for pharmacists or a patient reminder card crafted specifically for dispensing purposes. More than one-third of the surveyed pharmacists, who admitted not using the mentioned PPP measures, expressed their intention to adopt them in the future. This suggests that many pharmacists were unaware of the existence of these measures, but upon learning about them, showed some inclination toward incorporating them into practice. Notably, the reported use of pharmacist checklists and patient reminder cards during the dispensing of oral retinoids in community pharmacies was lower in Denmark compared to other European countries, as was the reported use of warning signs on outer packages [12]. The latter appeared to be the most utilized PPP measure in Denmark, yet it still lagged behind the European average: 49% compared to 68%, respectively [12]. These findings, along with the previously reported Denmark's less favorable results regarding PPP measures for valproate dispensing [13], suggest a need for increased efforts to raise awareness among Danish pharmacists about their role in ensuring the safe use of teratogenic medications. Furthermore, it is a call to explore ways to support adoption of PPP measures in Danish community pharmacies.

Among Danish patients, similarly as among the patients from other European countries [12], the most frequently utilized PPP related to oral retinoid use was the PIL included in the medication package. This suggests that, in general, patients are inclined to read the PIL of the medication they use. However, the thoroughness of reading the PILs may vary [16], as it was indicated by the limited number of patients in the European study who noticed the QR code in the PIL, providing more information about teratogenicity of oral retinoids [12]. Consequently, information from physicians or pharmacists regarding critical side effects, such as teratogenicity, is crucial and complements the importance of informative PILs or visual aids on outer packaging. In Denmark, pregnancy consultations and the use of the visuals on the outer package were, respectively, the second and third most frequently reported PPP measures used by patients. Additionally, the reported use of these PPPs by patients in Demark was among the highest if compared to other European countries [12], which

aligns well with high level of teratogenicity risk awareness among Danish patient using oral retinoids.

4.1 | Strengths and Limitations

The strength of this study lies in the inclusion of a diverse range of participants, encompassing prescribers, pharmacists, and patients. Consequently, the study offers insights into pregnancy prevention practices in the processes of prescribing, dispensing, and using oral retinoids. However, certain limitations common to general surveys need to be mentioned.

First, recall bias and social desirability bias cannot be dismissed. Recall bias could occur when participants recollected when and from whom they first learned about the teratogenic effects of oral retinoids. To mitigate this bias, the study exclusively included patients who had used oral retinoids within the past 5 years. Social desirability bias may have manifested in the form of an overestimation of awareness and adherence to PPP measures. On the positive side, the questionnaires were both anonymous and self-administered, reducing the likelihood of respondents feeling pressured to provide socially desirable responses.

Second, selection bias could impact the generalizability of the study's results. As per available data, there are more than 3000 GPs, over 90 dermatology practices, and more than 500 community pharmacies in Denmark [17, 18]. This suggests that less than 1% of Danish GPs, dermatologists from around one-third of practices, and pharmacies from nearly one-fifth of pharmacies responded to the survey. To mitigate the selection bias among GPs, an attempt was made to implement probability sampling among GPs by telephoning a randomly selected sample. However, this approach proved inefficient as most GPs were not motivated to participate, suggesting that even when using probability sampling, selection bias remains a concern, as only motivated individuals typically respond. The recruitment process, conducted through certain societies or social media forums, inherently excluded individuals not affiliated with these groups. Additionally, relying on Facebook groups as a source may have skewed the sample toward a younger demographic, as younger individuals are known to use social media more frequently than their older counterparts [19]. According to the Danish Statistics, both GPs and dermatologists in Denmark tend to be in the age group of 45–64 years. Meanwhile, a majority of physicians in our survey had 11–20 years of experience, possibly being under 50 years of age. Regarding patients, in Denmark more than 8000 women in age group of 18–44 (with more in age group 18–24 than 25–44 years) purchased isotretinoin—the most popular oral retinoid—during year 2019 [20]. Hence, less than 1% of the potential target population responded to the survey. On the other hand, the proportion of different kinds of retinoids used by study participants was very close to the proportion among all the women of reproductive age using oral retinoids in Denmark: for isotreinoin—98% in the study versus 99% nationally, and for acitretin—2% in the study versus 1% nationally [20]. Finally, the study was conducted during the COVID-19 pandemic, which may have reduced the willingness of HCPs and women to participate in the survey due

TABLE 5 | The use of education materials from the PPP by pharmacists, *N* (%), *N* total = 87.

Use of educational materials	Check list for community pharmacists	HCP guide	Warning sign on the outer package	Patient reminder card	DHPC
Yes	5 (5.7%)	8 (9.2%)	43 (49.4%)	1 (1.1%)	11 (12.6%)
Not sure/no	82 (94.3%)	79 (90.8%)	45 (51.7%)	86 (98.9%)	76 (87.4%)
If no, likely to use in the future	27 (31.0%)	16 (18.4%)	31 (35.6%)	17 (19.5%)	19 (21.8%)
If no, unlikely to use in the future	24 (27.6%)	28 (32.2%)	6 (6.9%)	38 (43.7%)	31 (43.7%)

Abbreviations: DHPC = direct healthcare communication, HCP = health care professional.

TABLE 6 | Pharmacists' practices when dispensing oral retinoids to women in reproductive age, *N* (%), *N* total = 80.

Practices while dispensing	Always/often	Never/seldom
Inform about effective contraception	63 (78.8%)	17 (21.3%)
Advice stopping treatment when pregnant	47 (58.8%)	33 (41.3%)
Advice to contact doctor when suspect a pregnancy	59 (73.8%)	21 (26.3%)
Inform about pregnancy testing before/during/after treatment	55 (68.8%)	25 (31.3%)

TABLE 7 | Characteristics of the patients, *N* = 50.

Characteristics		*N* (%) unless otherwise indicated
Age	Mean (SD)	26.1 (6.90)
	Median (IQR)	25 (22–28)
	Range	16–46
Education	Primary school	16 (32.0%)
	Secondary school	21 (42.0%)
	Professional school	9 (18.0%)
	University	21 (42.0%)
	Other	3 (6.0%)
Medication use status		
Isotretinoin or Accutane	I have used it before	14 (28.0%)
	I am currently using it	36 (72.0%)
	I have never used it	0 (0.0%)
	I don't remember	0 (0.0%)
Acitretin or Neotigason	I have used it before	1 (2.0%)
	I am currently using it	0 (0.0%)
	I have never used it	48 (96.0%)
	I don't remember	1 (2.0%)
Toctino	I have used it before	0 (0.0%)
	I am currently using it	0 (0.0%)
	I have never used it	48 (96.0%)
	I don't remember	2 (4.0%)

to other healthcare challenges. We mitigated this issue by extending the initially planned data collection period.

5 | Conclusions

The study revealed that in Denmark, physicians, pharmacists, and medicine users were cognizant of the teratogenic effects associated with oral retinoids. However, adherence to and impact of the pregnancy prevention measures varied across the different measures. The RAF requiring signatures was the least favored measure among physicians, reflecting cultural aspects within the Danish healthcare system. The pharmacist checklist was underutilized, likely due to a lack of awareness about its existence. This underscores the importance of enhancing the dissemination and feasibility of measures targeting community pharmacies. Patients primarily relied on information found on medication packages and received guidance through pregnancy prevention consultations with HCPs. Therefore, an improvement in adherence to pregnancy prevention measures by physicians and pharmacists who consult their patients while prescribing and dispensing oral retinoids could lead to heightened awareness and the safer usage of oral retinoids by patients and should be enhanced in future research and practice efforts.

5.1 | Plain Language Summary

Oral retinoids are medications used to treat severe skin conditions, but they can harm a developing baby if taken during

TABLE 8 | Patients' experiences of the PPP, $N = 50$.

Experience of the PPP by patients	Yes, *N* (%)
Received the patient card with appointments	3 (6.0%)
Reviewed the RAF	5 (10.0%)
Singed the RAF	4 (8.0%)
Read the patient information leaflet (PIL)	45 (90.0%)
Saw a warning sign on the outer medication package	25 (50.0%)
Discussed the use of contraception	36 (72.0%)
Oral retinoid changed to other treatment	1 (2.0%)
Pregnancy testing before treatment with oral retinoids	23 (46.0%)
Pregnancy testing during treatment with oral retinoids	24 (48.0%)
Pregnancy testing after treatment with oral retinoids	2 (4.0%)

pregnancy. To prevent this, the European Medicine Agency (EMA) created guidelines for physicians, pharmacists, and women on how to avoid using oral retinoids during pregnancy. The guidelines refer to the use of the pregnancy prevention measures such as healthcare professionals' and patients' guides, pharmacist checklists, risk acknowledgment forms, requirements for pregnancy testing, and consultations on birth control. Our study looked at how much physicians, pharmacists, and patients in Denmark knew about and used the pregnancy prevention measures, when prescribing, dispensing, and using oral retinoids. We surveyed dermatologists, general practitioners, pharmacists, and women who had used oral retinoids in the past 5 years. Nearly everyone who responded knew about the risks related to oral retinoid use during pregnancy. However, the use of different pregnancy prevention measures varied. Physicians mainly used patients' and healthcare professionals' guides. Pharmacists mostly relied on warning labels on medication packages. Most women read the medication leaflet, but few used other resources. This suggests that some of the pregnancy prevention measures related to oral retinoid use might need to be made easier to access and operate with.

Ethics Statement

According to Danish law, a formal ethical assessment was not necessary, as the study did not collect any biological material. Data was stored according to the policy of the University of Copenhagen which follows the national legislation and the requirements of the General Data Protection Regulation (GDPR).

Conflicts of Interest

The authors declare no conflicts of interest.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.