



Commission  
on Human  
Medicines

Independent report

**REPORT OF THE COMMISSION ON HUMAN  
MEDICINES ISOTRETINOIN EXPERT WORKING  
GROUP**

**26 April 2023**

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## Executive summary

Isotretinoin is an effective treatment for severe acne which has not responded to standard treatments. The product information for isotretinoin includes warnings and guidance regarding the use of isotretinoin. This includes details about the monitoring requirements for all patients as well as information about possible side effects. There have been ongoing patient concerns about the safety of isotretinoin, more recently regarding the persistence of some suspected psychiatric and sexual adverse effects after isotretinoin has been stopped.

This report of the Commission on Human Medicines Isotretinoin Expert Working Group outlines the data considered, the review process and the resulting recommendations of the review of psychiatric and sexual side effects suspected to be associated with the treatment for severe acne, isotretinoin.

In terms of the data considered, the Isotretinoin Expert Working Group (EWG) held eight meetings to consider the available evidence from published studies and the Yellow Card (YC) scheme via which patients and families have submitted reports of suspected adverse reactions, as well as information provided by stakeholders through the call for information and heard directly from patients, their families and other stakeholders through three dedicated Isotretinoin EWG meetings.

The review considered the complex relationship between isotretinoin, severe acne, mental health and sexual health. The review concluded that the overall balance of risks and benefits for isotretinoin remains favourable but further action should be taken to ensure patients are fully informed about isotretinoin and are effectively monitored during and after treatment. Limitations in the data, including conflicting study data, lack of consistent patient level data or long term follow up information prevented the establishment of causal associations between the acute and longer term psychiatric and sexual side effects and the use of isotretinoin.

Following consideration of the data, the Commission on Human Medicines (CHM) has advised to further strengthen safety measures for isotretinoin with updates to warnings and the list of side effects in the product information of isotretinoin. More specifically, and in addition to the existing warnings, the CHM advised the following.

The product information should be amended to state that initiation of isotretinoin treatment in those under 18 years of age should require the agreement of 2 prescribers. This level of supervision is not currently required for any other medicine prescribed by dermatologists. The practical aspects of this advice are being explored and will be implemented following consideration by a range of stakeholders represented in the CHM's Expert Group on implementation of the CHM advice on isotretinoin.

The product information should be strengthened to include new warnings about sexual dysfunction which may continue after treatment with isotretinoin has stopped and that the warnings about psychiatric disorders will be revised to reflect the unknown frequency with which these may occur.

The product information will explicitly state that patients, and where applicable their families, must be counselled about the risk of psychiatric side effects and sexual dysfunction prior to prescription of isotretinoin, and ideally prior to any referral that might include consideration of isotretinoin treatment. Patients should have an assessment of their mental health prior to treatment and should be monitored during treatment for developing psychiatric or sexual disorders.

The CHM advised that the risk management plan for isotretinoin, which outlines the requirements for the marketing authorisation holders (MAHs) should include:

- Revised risk minimisation materials including the risk acknowledgement form to be provided to all patients (currently these additional materials are only provided to female patients).
- The need for further research to gain greater insight into the adverse events associated with isotretinoin, including the risks of psychiatric and sexual side effects and the study of any potential long-term effects in adulthood.

The Medicines and Healthcare products Regulatory Agency will work to implement the CHM's recommendations. The CHM will establish an implementation group which includes relevant stakeholders to aid implementation of the recommendations.

## 1. INTRODUCTION

The Government's independent advisory committee, the Commission on Human Medicines (CHM) reconvened the Isotretinoin Expert Working Group (EWG) in September 2019 following concerns raised by patients and other stakeholders about the risks of psychiatric (mental health) side effects and sexual side effects associated with the use of isotretinoin for the treatment of acne. The Isotretinoin EWG had last met in July 2014 to consider psychiatric side effects suspected to be associated with the use of isotretinoin.

EWGs provide advice to the CHM by bringing together relevant experts and providing a forum for discussion of all available information on a specific medicinal product(s) or safety issue. Any conclusions and recommendations are then reported to the CHM, which in turn advises the Medicines and Healthcare products Regulatory Agency (MHRA) and relevant Ministers on whether regulatory action is needed to optimise the safe use of a medicine.

This report summarises the information considered by the Isotretinoin EWG in their meetings between March 2020 and October 2021 and outlines the findings in relation to those areas.

In addition to this scientific report, a [plain language summary](#) is available on our website. Also available to support this report on the [MHRA's website](#) are the recordings of the presentations from stakeholders to the Isotretinoin EWG held in July 2021 and finally the recording of the presentation of the data considered by the Isotretinoin EWG to CHM in December 2021<sup>1</sup>.

This chapter outlines the background to the review and the establishment of the Isotretinoin Expert Working Group. It provides information about isotretinoin, acne, the current position on psychiatric and sexual side effects, the membership of the Isotretinoin EWG, its remit and the scope of its work.

### 1.1. Background to the review

#### 1.1.1. Isotretinoin

Isotretinoin belongs to the class of chemical compounds called retinoids and is a licensed treatment for severe acne. It should only be prescribed by physicians with expertise in the use of systemic retinoids<sup>2</sup> to treat **severe** forms of acne that have not responded to other treatments, such as antibiotics and topical treatments (creams or gels). Isotretinoin capsules are also known by the brand names Roaccutane, Reticutan, and Rizuderm in the UK, and are known as Accutane and other brand names in other countries. Rizuderm is not currently marketed in the UK.

In addition to beneficial effects on acne, isotretinoin can cause side effects in some people, and in some cases, these can be unpredictable and severe. Details about the possible side effects, including psychiatric and sexual effects are provided in the product information which consists of the Summary of Product Characteristics (SmPC) for prescribers and the Patient Information Leaflet (PIL) which accompanies the medicine.

Isotretinoin is marketed in many countries worldwide and there may be differences in the way that isotretinoin is prescribed as well as differences in the information supplied with the medicine. To

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<sup>1</sup> Please note that the recordings of the meetings have been redacted to reflect the consent of attendees.

<sup>2</sup> The Summary of Product Characteristics (SmPC) states 'Isotretinoin should only be prescribed by or under the supervision of physicians with expertise in the use of systemic retinoids for the treatment of severe acne and a full understanding of the risks of isotretinoin therapy and monitoring requirements.' In the UK this has been interpreted to mean under the supervision of a consultant dermatologist. (British Association of Dermatology: <https://www.bad.org.uk/pils/isotretinoin/>)

date, the MHRA is not aware of any country where isotretinoin products have been removed from a market due to safety concerns. However, individual products have been withdrawn in some countries for commercial reasons.

### **1.1.2. Acne Vulgaris**

Acne vulgaris is a chronic inflammatory disease and is among the most common dermatological conditions worldwide. An estimated 9.4% of the global population are affected by acne (Tan & Bhate, 2015), with 20 to 35% of these developing moderate or severe acne (Williams, Dellavalle, & Garner, 2012). Prevalence varies greatly, with higher rates of acne in developed countries compared with developing countries (some of which report no acne at all) (Cordain, et al., 2002), and in some studies an urban/rural disparity has also been noted (Sutaria, Masood, & Schlessinger, 2021).

Research in the US has shown that 85% of people between the ages of 12 and 24 years have acne at some point, and while it is most common in teenagers, acne affects 8% of adults aged 25 to 34 years and 3% of adults aged 35 to 44 years. Acne in young adults may represent continuation of adolescent acne or development of late-onset disease (Yentzer, et al., 2010). Acne is more common in men during adolescence (ranging from 81 to 95 percent in young men and 79 to 82 percent in young women) but in adulthood, incidence is higher in women (Skroza, et al., 2018).

Acne is one of the most common skin conditions in the UK, leading to 3.5 million visits to primary care every year (Dawson, 2013). Prevalence estimates across the literature are generally difficult to compare due to differing definitions of acne and acne severity used between studies and variation in the availability and use of acne treatments (Williams, Dellavalle, & Garner, 2012), (Moradi Tuchayi, et al., 2015).

The pathogenesis of acne is not completely understood but is thought to involve several processes. The main pathogenic factors contributing to the condition are sebaceous gland hyperplasia and excess sebum production, abnormal follicular differentiation, *Cutibacterium (Propionibacterium) acnes* colonisation, and inflammation and immune response. External factors may also contribute to acne, including the use of cosmetics, topical corticosteroids, and oral medicines (corticosteroids, lithium, iodides, some antiepileptic drugs) (Dellavalle & Howland, 2017).

Predictors of acne severity include early onset of comedonal acne and a number of family members with a history of acne (Ghods, Orawa, & Zouboulis, 2009). Factors that can cause acne to flare include the menstrual cycle, picking, and emotional stress (Dellavalle & Howland, 2017).

There is currently no single uniform, standardised, and reproducible grading system for the severity of acne. Acne is commonly classified by type (comedonal/papular, pustular/nodulocystic) and/or severity (mild/moderate/moderately severe/very severe). Skin lesions can be described as inflammatory or non-inflammatory (Dellavalle & Howland, 2017). Grading of acne may involve lesion counting and photographic methods. A number of qualitative and quantitative instruments have been developed. However, there is a lack of consensus on the exact grading criteria, which hampers the conduct and comparison of randomised controlled clinical trials evaluating treatments and outcomes (Moradi Tuchayi, et al., 2015).

Prevention of acne relies on the successful management of modifiable risk factors, such as underlying systemic diseases and lifestyle factors (Moradi Tuchayi, et al., 2015). For secondary prevention, general good skin care techniques should be emphasised (Dellavalle & Howland, 2017).



### **1.1.3. Place of isotretinoin in the management of acne vulgaris**

Isotretinoin is authorised for the treatment of severe forms of acne (such as nodular or conglobate acne or acne at risk of permanent scarring) resistant to adequate courses of standard therapy with systemic anti-bacterials and topical therapy.

Currently Isotretinoin should only be prescribed by or under the supervision of physicians with expertise in the use of systemic retinoids for the treatment of severe acne and a full understanding of the risks of isotretinoin therapy and monitoring requirements.

In the UK, this has been interpreted in clinical guidance to mean isotretinoin must be prescribed by or under the supervision of a consultant dermatologist.<sup>4</sup>

Isotretinoin is not suitable for all patients and there are extensive warnings in the product information outlining the monitoring requirements as well as the possible side effects which may occur and the actions that may need to be taken to support the patient.

The National Institute of Health and Care Excellence (NICE) published a guideline on the management of acne vulgaris (NG198) on the 25 June 2021<sup>3</sup>. This is the first NICE guideline on acne; previously the British Association of Dermatologists issued guidance in 2010<sup>4</sup> which was endorsed by NICE. Consistent with the regulatory position, the NICE recommendation for the use of isotretinoin in severe acne and isotretinoin is not listed as a first line treatment for acne.

There are currently no other medicinal treatment options for severe acne.

### **1.1.4. Authorisation status of isotretinoin and product information in the UK**

Isotretinoin was first authorised in 1983 under the brand name Roaccutane for Roche. Currently in the UK, three generic products are authorised to Generics (UK) Ltd, Ennogen Healthcare Ltd and Sun Pharmaceutical Industries Europe BV. In the past, there have been other generic brands of isotretinoin marketed in the UK but these are no longer authorised.

Isotretinoin should not be used for the treatment of prepubertal acne and is not recommended in children less than 12 years of age due to a lack of data on efficacy and safety. The dose of isotretinoin prescribed is individualised for each patient based on the patient's body weight and how they respond to treatment. Clear guidance regarding the dosing regimen is provided in the product information.

There have been warnings about the possible risks of psychiatric disorders in the product information since the 1990's. These have been updated as the result of previous European reviews. The current warnings in the SmPC and PIL for isotretinoin products are outlined below.

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<sup>3</sup> [Recommendations | Acne vulgaris: management | Guidance | NICE](#)

<sup>4</sup> <https://www.bad.org.uk/healthcare-professionals/clinical-standards/clinical-guidelines/isotretinoin-acne>

## Summary of Product Characteristics (SmPC)

Section 4.4 of the SmPC includes the following warning about psychiatric disorders.

### **Psychiatric disorders**

Depression, depression aggravated, anxiety, aggressive tendencies, mood alterations, psychotic symptoms, and very rarely, suicidal ideation, suicide attempts and suicide have been reported in patients treated with isotretinoin (see section 4.8). Particular care needs to be taken in patients with a history of depression and all patients should be monitored for signs of depression and referred for appropriate treatment if necessary. However, discontinuation of isotretinoin may be insufficient to alleviate symptoms and therefore further psychiatric or psychological evaluation may be necessary.

Awareness by family or friends may be useful to detect mental health deterioration.

Section 4.8 of the SmPC lists the following psychiatric disorders and sexual disorders as possible side effects.

| Psychiatric disorders                               |   |
|---|---|
| Rare<br>(frequency $\geq 1/10,000$ to $< 1/1,000$ ) | Depression<br>Depression aggravated<br>Aggressive tendencies<br>Anxiety<br>Mood alterations                     |
| Very rare<br>(frequency $< 1/10,000$ )              | Suicide<br>Suicide attempt<br>Suicide ideation<br>Psychotic disorder<br>Abnormal behaviour                      |
| Reproductive system and breast disorders            |   |
| Frequency not known*                                | Sexual dysfunction including erectile dysfunction and decreased libido<br>Gynaecomastia<br>Vulvovaginal dryness |

Extract from UK SmPC dated 27/3/22

## **Patient Information Leaflet (PIL)**

### Section 2 **What you need to know before you take isotretinoin**

#### **Warnings and precautions**

Talk to your doctor or pharmacist before taking isotretinoin:

- If you have ever had any kind of mental health problems. This includes depression, aggressive tendencies or mood changes. It also includes thoughts about hurting yourself or ending your life. This is because your mood may be affected while taking Roaccutane.

#### **Additional precautions**

##### **Mental health problems**

You may not notice some changes in your mood and behaviour and so it is very important that you tell your friends and family that you are taking this medicine. They may notice these changes and help you quickly identify any problems that you need to talk to your doctor about.

##### **Advice for all patients**

- **Tell your doctor if you have ever had any mental illness** (including depression, suicidal behaviour or psychosis), or if you take medicines for any of these conditions.

### Section 4 **Possible side effects**

#### **Mental problems**

##### **Rare effects** (*may affect up to 1 in every 1,000 people*)

- Depression or related disorders. Signs of this include sad or altered mood, anxiety, feelings of emotional discomfort,
- Existing depression getting worse.
- Becoming violent or aggressive.

##### **Very rare effects** (*may affect up to 1 in every 10,000 people*)

- Some people have had thoughts about hurting themselves or ending their own lives (suicidal thoughts), have tried to end their own lives (attempted suicide), or have ended their lives (suicide). These people may not appear to be depressed.
- Unusual behaviour.
- Signs of psychosis: a loss of contact with reality, such as hearing voices or seeing things that are not there.

#### **Contact your doctor straight away if you get signs of any of these mental problems.**

Your doctor may tell you to stop taking isotretinoin. That may not be enough to stop the effects: you may need more help, and your doctor can arrange this.

#### **Other side effects**

##### **Unknown frequency:** (*frequency cannot be estimated from the available data*)

- Problems getting or maintaining an erection
- Lower libido
- Vaginal dryness

Extract from UK PIL dated March 2022

### **1.1.5. Other uses for isotretinoin**

Isotretinoin has only ever been authorised for the treatment of acne. However, it has been used in clinical trials and in individual patients to treat a variety of other skin conditions. Isotretinoin has also been used to treat certain types of cancer such as neuroblastoma.

Use of a medicine such as isotretinoin for unauthorised conditions is referred to as off-label use. Medicines can be used off-label if the prescriber considers it to be of benefit to the patient. The prescriber takes on additional responsibilities when prescribing medicines off-label. This review focused on the authorised use of isotretinoin, however, the risks apply to any use of the medicine and all patients should be informed about the risks and monitored appropriately.

### **1.1.6. Previous reviews of isotretinoin**

In addition to the routine methods for monitoring the safety of medicines, isotretinoin has been subject to a number of additional reviews at both a UK and EU level.

In 2002, all oral isotretinoin products were subject to a Europe-wide review which was led by the UK and focussed on providing accurate and consistent product information for prescribers and patients across Europe (an Article 29 referral and an Article 30 referral procedure).

The Article 29 and 30 referral procedures did not include an evaluation of safety but given concerns regarding possible psychiatric side effects it was agreed at a European level during the referral discussions that a separate evaluation of this issue was needed. The marketing authorisation holders (MAHs) were requested to submit an evaluation of psychiatric side effects suspected to be associated with isotretinoin.

The Isotretinoin Working Group of the Commission on Safety of Medicines (CSM) (the predecessor of the CHM) first considered this issue in August 2003 and proposed that suicidal ideation, depression aggravated, anxiety, aggression and mood alteration should be added to the warnings provided for isotretinoin. These additions were discussed and subsequently agreed at a European level before being incorporated into the product information for all oral isotretinoin products.

A further European review was undertaken by the UK in June 2005. The review aimed to address outstanding issues relating to the risk of psychiatric disorders, including a detailed analysis of data considering age and gender, dose and duration of treatment in relation to reactions, patient's past medical history (and family history) and confounding factors with a sub-analysis of positive de-challenge and re-challenge cases.

The review tried to evaluate whether there was a relationship between poor responders (individuals with acne that did not improve with isotretinoin treatment), the severity of the acne or the dose of isotretinoin and the occurrence of psychiatric side effects. Unfortunately, due to limitations in the data, it was not possible to establish, with a reasonable degree of certainty, any specific trends or associations with these factors.

In 2005, the CSM's Isotretinoin Working Group concluded that the warnings in the product information implemented in 2003 adequately reflected the available data and did not recommend any further amendments to the SmPC. However, significant updates were made to the patient information leaflet to improve readability. Healthcare professionals including the British Association of Dermatologists were advised that patients treated with isotretinoin should be informed about the risk of possible mood changes and monitored for signs of depression and referred for appropriate treatment if necessary.

The risk of psychiatric side effects was kept under review and in 2014 in the light of accumulating concerns regarding psychiatric side effects, particularly depression and suicidal behaviours suspected to be associated with isotretinoin, the CHM agreed it was timely to review the available data

regarding the risk of psychiatric side effects associated with isotretinoin. In 2014, the CHM established the Isotretinoin Expert Working Group<sup>5</sup> which considered all the available data on psychiatric side effects suspected to be associated with the use of isotretinoin. Due to limitations in the data it was not possible to establish a causal association with isotretinoin, however the information was considered sufficient to support the warnings in the product information. As a result of the review, recommendations were made regarding the importance of informing patients of the risk of psychiatric side effects and that this information should be shared with family and friends as the patient may not notice some of the changes in their mood and behaviour. In addition to updating the product information, healthcare professionals were reminded about the possible risk of psychiatric disorders<sup>6</sup>.

A reminder on who should prescribe isotretinoin was issued in the August 2007 edition of the MHRA's monthly bulletin Drug Safety Update<sup>7</sup>. This article was republished in December 2014 when the MHRA moved content to the GOV.UK website. A further Drug Safety Update article was issued to healthcare professionals in December 2014 to remind of the possible risk of psychiatric side effects. At the same time, guidance for patients was published on the MHRA website<sup>8</sup> regarding the use and side effects of isotretinoin.

Psychiatric side effects were also considered within a Europe-wide review for isotretinoin and other oral retinoids which completed in March 2018. The review primarily evaluated the Pregnancy Prevention Programme materials which were in place due to the teratogenic risk associated with isotretinoin and resulted in streamlining and improvements to the risk minimisation materials. The review of psychiatric side effects resulted in consistent warnings being implemented across all retinoids but did not recommend any further regulatory action for isotretinoin at that time<sup>9</sup>.

MHRA started to receive increasing numbers of reports of erectile dysfunction from 2012. These cases were closely monitored and a Europe wide review of all cases reported with side effects relating to sexual function and fertility disorders was conducted in 2017 and resulted in the product information being updated to list sexual dysfunction, including erectile dysfunction and loss of libido as possible side effects. The updated information was communicated to healthcare professionals in the UK via an article in the October 2017 edition of MHRA's monthly bulletin Drug Safety Update<sup>10</sup>.

The MAHs are legally required to produce regular periodic safety update reports (PSUR). The objective of the PSUR is to present a comprehensive and critical analysis of the risk-benefit balance of the product taking into account new or emerging safety information in the context of cumulative information on risk and benefits. A PSUR assessment can determine if further investigations on a specific issue are needed, or if an action is necessary to protect public health (for example, an update of the information provided to healthcare professionals and patients). The 2019 PSUR for isotretinoin resulted in the product information being updated to include vulvovaginal dryness<sup>11</sup> as a possible side effect which may also have an impact on a patient's sex life.

The previous reviews of isotretinoin undertaken by the MHRA did not include direct involvement from a wide range of stakeholders such as those who have taken isotretinoin and their families. This most recent review provided an opportunity to consider all available data once again on the risk of psychiatric side effects and in addition to thoroughly evaluate the data relating to sexual side effects.

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<sup>5</sup> <https://assets.publishing.service.gov.uk/media/5492db7ce5274a42900002f2/DSU2.pdf>

<sup>6</sup> <https://www.gov.uk/drug-safety-update/isotretinoin-roaccutane-reminder-of-possible-risk-of-psychiatric-disorders>

<sup>7</sup> <https://www.gov.uk/drug-safety-update/isotretinoin-for-severe-acne-who-should-prescribe-it>

<sup>8</sup> <https://www.gov.uk/government/publications/isotretinoin-for-severe-acne-uses-and-effects/isotretinoin-for-severe-acne-uses-and-effects>

<sup>9</sup> [Retinoid-containing medicinal products | European Medicines Agency \(europa.eu\)](https://www.ema.europa.eu/en/documents/psusa/isotretinoin-oral-formulations-cmdh-scientific-conclusions-grounds-variation-amendments-product/00010488/201905_en.pdf)

<sup>10</sup> [Isotretinoin \(Roaccutane\): rare reports of erectile dysfunction and decreased libido - GOV.UK \(www.gov.uk\)](https://www.gov.uk/drug-safety-update/isotretinoin-roaccutane-rare-reports-of-erectile-dysfunction-and-decreased-libido)

<sup>11</sup> [https://www.ema.europa.eu/en/documents/psusa/isotretinoin-oral-formulations-cmdh-scientific-conclusions-grounds-variation-amendments-product/00010488/201905\\_en.pdf](https://www.ema.europa.eu/en/documents/psusa/isotretinoin-oral-formulations-cmdh-scientific-conclusions-grounds-variation-amendments-product/00010488/201905_en.pdf)

Alongside the scientific data, it was agreed that it was important that the views of and information provided by patients and other stakeholders were sought and incorporated into decision making.

### **1.1.7. Regulatory position of isotretinoin in other countries**

In other countries there may be differences in the way isotretinoin is prescribed as well as differences in the product information and additional risk minimisation materials that may or may not be provided with the medicine.

In the USA, the MAHs all contribute to the iPLEDGE scheme<sup>12</sup> which is focussed on pregnancy prevention and integrated into the health insurance schemes. In the USA, prescribers must be registered with the iPLEDGE scheme but there are no restrictions associated with the expertise or specialism of the prescriber.

The iPLEDGE scheme includes various documents, of these the Patient Introductory Brochure provides information about isotretinoin as well as details about the risk of birth defects and the risk of serious mental health problems. The medication guide includes two consent forms that must be signed before starting treatment. The first is for all patients and the second is for female patients of childbearing potential. There continue to be reports of pregnancies in the USA despite the iPLEDGE scheme.

There are differences in clinical practice between the UK and the USA, including how consent is given and recorded. The General Medical Council has issued guidance regarding consent and how it should be recorded for medicines in the UK.

The FDA<sup>13</sup> have issued updates about the iPLEDGE scheme, alerts regarding suicidal thoughts or actions and a warning on the dangers of buying isotretinoin over the internet.

The isotretinoin medication guide in the USA includes the following warnings regarding psychiatric side effects outlined in the text box below.

There are currently no warnings regarding sexual side effects in the USA.

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<sup>12</sup> <https://www.ipledgeprogram.com/iPledgeUI/patientInfo.u>

<sup>13</sup> <https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/isotretinoin-marketed-accutane-capsule-information>

## Psychiatric Disorders

<brand name> may cause depression, psychosis and, rarely, suicidal ideation, suicide attempts, suicide, and aggressive and/or violent behaviors. No mechanism of action has been established for these events (see SIDE EFFECTS, Psychiatric).

Prescribers should read the brochure, *Recognizing Psychiatric Disorders in Adolescents and Young Adults: A Guide for Prescribers of Isotretinoin*. Prescribers should be alert to the warning signs of psychiatric disorders to guide patients to receive the help they need.

Therefore, prior to initiation of <brand name> therapy, patients and family members should be asked about any history of psychiatric disorder, and at each visit during therapy patients should be assessed for symptoms of depression, mood disturbance, psychosis, or aggression to determine if further evaluation may be necessary.

Signs and symptoms of depression, as described in the brochure (“Recognizing Psychiatric Disorders in Adolescents and Young Adults”), include sad mood, hopelessness, feelings of guilt, worthlessness or helplessness, loss of pleasure or interest in activities, fatigue, difficulty concentrating, change in sleep pattern, change in weight or appetite, suicidal thoughts or attempts, restlessness, irritability, acting on dangerous impulses, and persistent physical symptoms unresponsive to treatment.

Patients should stop <brand name> and the patient or a family member should promptly contact their prescriber if the patient develops depression, mood disturbance, psychosis, or aggression, without waiting until the next visit. Discontinuation of <brand name> therapy may be insufficient; further evaluation may be necessary. While such monitoring may be helpful, it may not detect all patients at risk. Patients may report mental health problems or family history of psychiatric disorders. These reports should be discussed with the patient and/or the patient’s family. A referral to a mental health professional may be necessary. The physician should consider whether <brand name> therapy is appropriate in this setting; for some patients the risks may outweigh the benefits of <brand name> therapy.

### *Side effects*

#### Psychiatric

Suicidal ideation, suicide attempts, suicide, depression, psychosis, aggression, violent behaviors (see WARNINGS, PSYCHIATRIC DISORDERS), emotional instability.

Of the patients reporting depression, some reported that the depression subsided with discontinuation of therapy and recurred with reinstatement of therapy.

Extract from USA prescribing information dated Aug 2022

In 2016, Health Canada reminded healthcare professionals regarding the importance of preventing pregnancy while taking isotretinoin<sup>14</sup> and updated the product information for isotretinoin products in 2017 to include a warning about the risk of impotence<sup>15</sup>.

<sup>14</sup> <https://healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2016/60096a-eng.php>

<sup>15</sup> <https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/safety-reviews/summary-safety-review-oral-retinoid-products-assessing-potential-risk-erectile-dysfunction.html>

The Canadian isotretinoin product monograph includes the following warnings regarding psychiatric and sexual side effects. In addition, all patients are required to sign a consent form.

#### Serious Warnings and Precautions

All patients must sign the informed consent form prior to initiating therapy.

Psychiatric: Some patients treated with ACCUTANE have become depressed and some attempted or committed suicide. Although a causal relationship has not been established, all patients should be screened and monitored for signs of depression before and during therapy (see WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests). Physicians should determine whether the patient may be depressed or has a history of depression including a family history of major depression before starting therapy with ACCUTANE.

If symptoms of depression develop or worsen during treatment with ACCUTANE, the drug should be discontinued promptly and the patient referred for appropriate psychiatric treatment as necessary. However, discontinuation of ACCUTANE may not alleviate symptoms and therefore further psychiatric or psychological evaluation may be necessary. A Psychiatric Assessment Checklist is available to assist physicians in screening patients for depression/suicidality prior to treatment and in monitoring for the development of psychiatric symptoms during treatment. This checklist is provided to the physician via the [www.acneandu.ca](http://www.acneandu.ca) website or by contacting the Roche Drug Information line at 1-888-762-4388.

Psychiatric See SERIOUS WARNINGS AND PRECAUTIONS BOX. Signs of depression, sad mood, hopelessness, feeling of guilt, worthlessness or helplessness, loss of pleasure or interest in activities, fatigue, difficulty concentrating, changes in sleep pattern, change in weight or appetite, suicidal thoughts or attempts, restlessness, irritability, acting on dangerous impulses, and persistent physical symptoms unresponsive to treatment. If symptoms of depression develop or worsen during treatment with ACCUTANE, the drug should be discontinued promptly and the patient referred for appropriate psychiatric treatment.

#### Side effects

Psychiatric Disorders: Depression, psychotic symptoms and, rarely, suicide attempts, suicide, and aggressive and/or violent behaviours (see SERIOUS WARNINGS AND PRECAUTIONS BOX, Psychiatric and WARNINGS AND PRECAUTIONS, Psychiatric). Depression has been reported during and after therapy. In some of these patients, depression has subsided with discontinuation of therapy and recurred when ACCUTANE therapy was reintroduced. Emotional instability has been reported with ACCUTANE.

Reproductive system: abnormal menses, erectile dysfunction.

Extract from Canadian Product Monograph dated May 2022

In Australia, the product information consists of the “Product Information” for healthcare professionals which follows the format of the SmPC in the UK and the Consumer Medicine Information (CMI) for patients<sup>16</sup>. The product information approved in Australia includes warnings similar to the UK in relation to psychiatric and sexual side effects.

<sup>16</sup> <https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/PICMI?OpenForm&t=&q=isotretinoin>



#### 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

##### Psychiatric Disorders

Depression, psychotic symptoms, and, rarely, suicide, suicidal ideation and attempts have been reported with Roaccutane. Particular care needs to be taken in patients with a history of depression and all patients should be monitored for signs of depression. Although no mechanism of action for these events has been established, discontinuation of Roaccutane may not alleviate symptoms and therefore further psychiatric or psychological evaluation may be necessary.

#### 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Psychiatric and central nervous system disorders: Behavioural disorders, depression, suicide attempt, suicide, (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE), headache, increased intracranial pressure (pseudotumour cerebri), seizures.

Reproductive system and breast disorders: Sexual dysfunction including erectile dysfunction and decreased libido, gynaecomastia. A causal association with these adverse effects has not been established.

Extract from Australian Product Information dated May 2019

## 1.2. The Isotretinoin Expert Working Group

In September 2019, the CHM advised that it was important to review the latest available data regarding the risk of psychiatric side effects as well as the risk of sexual dysfunction associated with isotretinoin, in order to evaluate their impact on the balance of benefits and risks of treatment.

The CHM therefore advised that the Isotretinoin EWG should be reconvened to consider whether further regulatory action was required to minimise these risks.

### 1.2.1. Scope of the review and terms of reference

The Isotretinoin EWG carefully considered the scope of the review at its first meeting in March 2020, particularly whether the proposed terms of reference addressed the full extent of the concerns raised by patients and their families. It was noted that patients had raised concerns about additional side effects, beyond psychiatric and sexual side effects. The majority of these concerns related to side effects which were recognised to be associated with isotretinoin and are listed in the product information. The Isotretinoin EWG also discussed that the safety of isotretinoin must be considered in the wider context of the benefits of treatment and risks associated with the underlying condition.

The terms of reference of the Isotretinoin EWG were finalised and adopted by the Isotretinoin EWG at its second meeting on 15 September 2020, as follows:

- a) To evaluate information from all available sources, including relevant stakeholders (patients, patient representatives, healthcare professionals, healthcare organisations, researchers, charity and patient organisations) on psychiatric effects suspected to be associated with isotretinoin. To consider whether regulatory action is required to minimise risk and ensure awareness of the risks.
- b) To evaluate information from all available sources, including relevant stakeholders (patients, patient representatives, healthcare professionals, healthcare organisations, researchers, charity and patient organisations) on sexual disorders suspected to be associated with isotretinoin. To consider whether regulatory action is required to minimise risk and ensure awareness of the risks.
- c) To consider the impact of the available information on psychiatric effects and sexual disorders on the balance of benefits and risks of isotretinoin.
- d) To consider what research could be undertaken to further elucidate any risks and long-term impact of psychiatric effects and sexual disorders and inform risk minimisation measures.
- e) To make recommendations to the Commission on Human Medicines to improve the balance of benefits and risks for isotretinoin, to raise awareness of the associated risks and for further research to evaluate the risks.

The Isotretinoin EWG met to consider the information relevant to its terms of reference on 12 March 2020, 15 September 2020, 5 May 2021, 16 July 2021, 21 July 2021, 17 August 2021 and 4 October 2021.

### **1.2.2. Membership**

The membership of the Isotretinoin EWG is published on the CHM web pages<sup>17</sup>. The Isotretinoin EWG included a lay representative and an expert in patient and public involvement in healthcare, as well as those with expertise in dermatology, psychiatry, epidemiology, pharmacoepidemiology, paediatric endocrinology, general practice, genetics, urology, andrology, and infertility. All members declared their interests and followed the conflict of interest's policy.

Professor Sir Munir Pirmohamed chaired the meetings on 12 March and 15 September 2020 and Professor Angela Thomas took over the chair of the subsequent meetings when Professor Sir Munir Pirmohamed had to step down from the Isotretinoin EWG after becoming the chair of the CHM.

Observers to the meetings were also invited from the NICE, the Primary Care Dermatology Society, NHS Improvement and the Care Quality Commission.

The Isotretinoin EWG fully recognised the importance of the patients' voice and supported the involvement of stakeholders who would be able to provide invaluable information about the risks of isotretinoin and their impact, as well as information on the differences in clinical practice and possible gaps in the implementation of current risk minimisation measures.

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<sup>17</sup> [Membership - Commission on Human Medicines - GOV.UK \(www.gov.uk\)](https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/90114/CHM_membership_2020.pdf)

## 2. INFORMATION FROM PATIENTS, FAMILIES AND OTHER STAKEHOLDERS

The importance of engaging with patients, their families and other relevant stakeholders was emphasised from the start of the review of psychiatric and sexual side effects suspected to be associated with isotretinoin.

This chapter describes how the views of patients, families and other stakeholders were sought and taken into account in the review and decision making.

### 2.1. Views of stakeholders

The MHRA continues to receive ongoing correspondence about concerns associated with the use of isotretinoin. Although the safety of isotretinoin has been continuously monitored and changes made to the product information to reflect the risks as they have been identified, the ongoing concerns of patients and their families suggested more needed to be done.

The Yellow Card scheme<sup>18</sup> receives information about suspected side effects and this information was an integral part of the assessment of psychiatric and sexual side effects which are discussed in more detail in chapters 4 and 5.

Given the sensitive nature of the psychiatric and sexual side effects being reviewed, it was considered important to gather stakeholder's views securely and systematically. A combination of communicating directly with identified stakeholders as well as promotion via social media (Facebook, twitter and LinkedIn) was used to try and ensure anyone who wished to could contribute to the review.

In order to be open and transparent, details of the review were published on GOV.UK<sup>19</sup> in November 2020. The webpage was also used to inform stakeholders about how to get involved as well as encouraging people who had experienced side effects to report them.

The Isotretinoin EWG's review focused on the situation in the UK, however, views from everyone, including those outside of the UK were welcomed.

The MHRA explored *how* and *what* information should be requested to support the review. Consideration was given to a structured survey to collect specific information on the nature of the side effects experienced and how the risks were managed. A survey was developed and shared with the Isotretinoin EWG and a selection of patient representatives. Feedback about the number of questions, level of detail requested and data protection were taken on board and the survey evolved into the public call for information.

In addition to the public call for information, patients and other stakeholders were given the opportunity to present to the Isotretinoin EWG. The level of interest was greater than anticipated and three meeting sessions were held to allow everyone who wished to the opportunity to present their views to the Isotretinoin EWG.

All information that was received by the MHRA for the attention of the Isotretinoin EWG was shared with the Isotretinoin EWG within the papers compiled by the MHRA and discussed at the Isotretinoin EWG meetings.

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<sup>18</sup> <https://yellowcard.mhra.gov.uk/information>

<sup>19</sup> [Isotretinoin: an expert review of suspected psychiatric and sexual side effects - GOV.UK \(www.gov.uk\)](https://www.gov.uk/government/news/isotretinoin-an-expert-review-of-suspected-psychiatric-and-sexual-side-effects)

## 2.2. Call for information

The MHRA issued a public call for information<sup>20</sup> on 10 November 2020. This was initially for 12 weeks but was extended for a further 2 weeks to accommodate the holiday period. The call for information closed 16 February 2021.

The call for information invited views on the following:

1. What is your view on the place of isotretinoin in the treatment of acne? We are interested in all views, both positive and negative.
2. What is your view of the risks associated with taking isotretinoin, particularly in relation to potential side effects such as psychiatric effects, including effects on mood or mental health and or sexual dysfunction including the ability to experience sexual pleasure?
3. What is your view on the measures currently in place to reduce the risks associated with isotretinoin?
4. In your opinion, what further measures could be taken to optimise the safe use of isotretinoin and raise awareness of the potential risks?

Responses were received via a secure online form which gave options to draft answers within the form and to upload supporting documentation. People who had experienced side effects to isotretinoin were also encouraged to report them through the Yellow Card scheme. Views were particularly sought from UK patients, however contributions from those living outside the UK were accepted. All contributions were assessed by the MHRA and were shared in full with the Isotretinoin EWG.

More information about the call for information can be found in Annex 1.

## 2.3. Presentations from patients, families and stakeholders

To aid assessment of the issues under consideration, the Isotretinoin EWG asked to hear directly from patients and other stakeholders on the following questions:

- Based on your experience of isotretinoin, what aspect of treatment has had the greatest impact (positive or negative)?
- How should the risks associated with isotretinoin be managed?

Details about the Isotretinoin EWG meeting were promoted through direct emails with everyone who had registered to receive notifications about the review, via the webpage and via social media. Individuals who wanted to contribute were asked to register interest by 17 June 2021. A total of 84 individuals asked to present to the Isotretinoin EWG and everyone who registered was invited to present at one of three meetings on 16 and 21 July. Support was offered to everyone wishing to present to the Isotretinoin EWG with preparatory meetings held to ensure everyone was familiar with the virtual meeting platform and how the meetings would run. Everyone was given a guidance

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<sup>20</sup> <https://www.gov.uk/government/consultations/isotretinoin-call-for-information-to-be-considered-as-part-of-an-expert-review>

note and a consent form to confirm how they wished to be addressed and whether their presentation could be included in the final recording published on the MHRA webpage.

Those who were not able to present to the Isotretinoin EWG and who had additional information to share were asked to send it to MHRA and this was shared with the Isotretinoin EWG.

### 2.3.1. Views expressed by stakeholders

The following themes were raised repeatedly in the call for information, written contributions and presentations.

*'I received the two course in different hospitals in England [locations redacted] and the experience was very different. My first course I had monthly reviews and it the approach taken was very professional and serious with concern of the possible side effects of the treatment however the second course was far more relaxed. I do feel that if I was unfortunate enough to have negative side effects it could have been easily undetected when receiving treatment at the second hospital.'*

*Comment received through call for information*

Patients and their families, whether their experience was positive or negative, called for clear information about side effects to be shared with patients before they started treatment with isotretinoin and regular monitoring of patients during treatment.

The patient's experience varied between clinics and this suggested a more consistent approach was needed so that patients and their families know what to expect and can make informed decisions.

Concern was raised that the information on the nature and frequency of side effects in the product information for isotretinoin was misleading and that the Yellow Card data underestimated the frequency of side effects due to underreporting.

*'These are rare but totally unpredictable, so you cannot assure patients that they will not be one of the unlucky ones who get the side effect. There are no tests that can be performed to predict one of these side effects.'*

*Comment received through call for information*

*'...but I fear this drug represents a lot more of a risk than present PIL guidelines suggest due to under-reporting of symptoms. A cursory look at online social media support groups of which I am a member suggests that people with chronic conditions due to a suspected link to isotretinoin are at perhaps in the tens of thousands in the English-speaking world alone...'*

*Comment received through call for information*

There was particular concern about the lack of awareness of sexual side effects and of the long-term nature of some side effects.

Some stakeholders felt that isotretinoin was prescribed inappropriately (to those who did not have severe acne) and that the side effects are unpredictable and can occur suddenly leaving patients vulnerable and the families lost, not knowing what to do.

Stakeholders reported a lack of acceptance among clinicians that isotretinoin might be causing the side effects they were experiencing and a lack of support for people experiencing side effects.

*'Never informed of the potential sexual side effects and would have found it very difficult to associate low libido with the drug without being informed.'*

*Comment received through call for information*

*'...it is not excusable to prescribe this drug with such strong effects on the whole body when only a few pimples (as in my case) are to be tackled.'*

*Comment received through call for information*

*'Currently, many of the teenagers given isotretinoin are given it for moderate or sometimes even mild cases of acne which is not nodulocystic.'*

*Comment received through call for information*

Some stakeholders did not consider isotretinoin safe enough for any patients to be prescribed it, while other stakeholders raised concerns about

*'If a patient asks their dermatologist about these effects, as I did myself, they are met with an immediate shutdown of any possibility that these symptoms will last, let alone even exist in the first place.'*

*Comment received through call for information*

*'Stop the use of this drug. Too many lives have been destroyed and too much damaged done'*

*'This drug should not be prescribed to children under 18. Adolescence brings hormonal imbalances resulting in mood swings which mean that those suffering and their carers are unable to identify psychiatric issues as they arise.'*

*Comments received through call for information*

whether isotretinoin was suitable for younger patients who may not fully understand the risks, with calls to restrict its use in those under the age of 18 years.

Other stakeholders emphasised the impact of severe acne on their lives and were concerned about the possibility of isotretinoin being taken off the market as a result of the review.

*'Through treatment with Isotretinoin, I have been able to get my life back. I cannot underestimate the value of Isotretinoin for people, like me, who suffer from severe acne. I don't think I'd be here now if it wasn't for Isotretinoin. That's the difference it's made to my life.'*

*'I will forever be grateful that this treatment was available to me and I'd feel disappointed for others in my shoes should the medicine be discontinued / removed from the market.'*

*Comments received through call for information*

Stakeholders raised concern about misinformation spread via social media and particularly beauty vloggers who may not discuss the negative effects of isotretinoin.

*'All patients receiving isotretinoin under my care receive a copy of the BAD patient information leaflet following discussion of the potential risks of treatment; they have a 'cool off' period prior to commencing isotretinoin and again the risks are discussed before starting treatment.'*

*Comment received through call for information*

A number of stakeholders called for a cooling off period between the patient being counselled about the side effects of isotretinoin and decision being made about initiating of treatment and the first prescription issued.

Stakeholders called for more research on the side effects of isotretinoin and how they could be treated.

The experiences and views expressed by stakeholders were of great importance to the Isotretinoin EWG and the ways in which they informed the final recommendations are outlined in Section 8.

*'I feel as people see the benefits on social media, they are not fully aware of the risks involved or may pass them off as insignificant due to the potential results'*

*Comment received through call for information*

*'More effort needs to be made to follow what happens AFTER people complete their course of Isotretinoin, to study the latent effects. You need to find out why so many people's health declines after taking it, in order to know how to protect young people going forwards.'*

*Comment received through call for information*

*'Another suggestion would be to provide this information to the patient on the first appointment, and give them a week to read through it, ask questions, and make sure they understand the risks, before actually starting treatment.'*

*Comment received through call for information*

### 3. MECHANISMS OF THERAPEUTIC ACTION AND ADVERSE EFFECTS OF ISOTRETINOIN

#### 3.1. Mechanisms of action for therapeutic effect

Isotretinoin (13-cis-retinoic acid) is a vitamin A derivative and a stereoisomer of all-trans retinoic acid (tretinoin). The exact mechanism of action of isotretinoin has not been elucidated in detail, but it has been established that the improvement seen in the clinical presentation of severe acne is associated with suppression of sebaceous gland activity and a histologically demonstrated (seen under a microscope) reduction in the size of the sebaceous glands. Furthermore, a dermal (skin) anti-inflammatory effect of isotretinoin has been established.

Isotretinoin inhibits proliferation of sebocytes (skin cells which produce sebum). Sebum (an oily substance produced in the sebaceous glands) is a major substrate for the growth of *Propionibacterium acnes* so reduced sebum production inhibits bacterial colonisation of the skin pores.

Isotretinoin impacts all of the major aetiological factors implicated in acne. It influences cell-cycle progression, cellular differentiation, cell survival and apoptosis (programmed cell death) of sebocytes and influences the hormones in the hypothalamo–pituitary axis.

13-cis-retinoic acid is an active form of vitamin A and related retinoids which play central roles in several physiologic processes such as embryonic development, proliferation, differentiation and apoptosis. Retinoids bind to retinoic acid receptor (RAR) and retinoid X receptor (RXR) families, altering transcriptional activity of these transcription factors from repressors to activators of gene expression. Like glucocorticoid and thyroid hormone receptors, RAR/RXRs are part of the nuclear receptor superfamily that regulates gene expression. RARs and RXRs play important functions in embryonic development, where concentration gradients of retinoic acid determine early morphogenetic patterns of differentiation and the development of various organs. Increasingly, the role of the retinoids is recognised in the physiology of the nervous system. RARs regulate expression of many different genes, in particular homeobox, or HOX genes whose proteins are crucial transcription factors in specifying the body plan during development and Forkhead box O (FoxO) transcription factors, which control programmes of gene expression that regulate apoptosis and cell-cycle progression, and oxidative stress resistance.

##### 3.1.1. Apoptosis (cell death)- sebocytes

Excessive production of sebum plays a major role in the way acne starts and develops. Isotretinoin exhibits a powerful sebum-suppressive effect which is thought to be based primarily on sebocyte apoptosis. Apoptosis is the death of cells which occurs as a normal and controlled part of an organism's growth or development. Isotretinoin's mechanism of action and some of its side effects have been postulated to be via its action on apoptosis via FoxO proteins.

FoxO transcription factors FoxO1, FoxO3a, FoxO4 and FoxO6 are important regulatory proteins that modulate the expression of genes involved in cell cycle control, DNA damage repair, apoptosis, oxidative stress, cell differentiation, glucose metabolism, inflammation, immune functions and regulation of stem cell homeostasis (Maiese, Chong, & Shang, 2008) (Li, et al., 2007) (Kim, et al., 2009) (Crossland, Constantin-Teodosiu, Gardiner, Constantin, & Greenhaff, 2008) (Mammucari, et al., 2007) (Sandri, et al., 2004), (Zhao, et al., 2007).

FoxO1 is the predominant isoform. FoxOs contain a conserved DNA binding domain and either inhibit or activate the transcription of target genes. FoxOs can also interact with other transcription factors like androgen receptors, thereby modifying gene regulation.



13-cis retinoic acid causes significant dose-dependent and time-dependent decreases in viable sebocytes. A portion of this decrease can be attributed to cell cycle arrest as shown by decreased DNA synthesis, increased p21 protein expression, and decreased cyclin D1 in SEB-1 sebocytes (Nelson, Gilliland, Cong, & Thiboutot, 2006).

Isotretinoin's effect on sebocyte apoptosis also results from isotretinoin-induced expression of the apoptotic protein tumour necrosis factor-related apoptosis-inducing ligand (TRAIL), insulin-like growth factor-binding protein-3 and neutrophil gelatinase-associated lipocalin.

Genetic variants or polymorphisms of components of the apoptotic signalling cascade, such as RARA (the gene for retinoic acid receptor alpha), might explain variations in the magnitude of isotretinoin induced apoptotic signalling and those patients with adverse effects of isotretinoin therapy or resistance to treatment. There are however currently no standard tests for genetic polymorphisms that could be incorporated into clinical practice to identify such differences.

[Figure 1 in the Medical Hypothesis paper](#) by (Melnik, 2016) shows the postulated mechanism of isotretinoin-induced apoptotic signalling to explain the pharmacological and side effects of isotretinoin.

It is proposed that many of the effects of isotretinoin are mediated by all-trans retinoic acid (ATRA) after isomerisation of the 13-cis isomer. After isomerisation of isotretinoin to ATRA and ATRA binding to RAR the transcription factor FoxO3a is unregulated. At the promoter level, FoxO3a induces the expression of TRAIL and FoxO1. TRAIL activates the caspase cascade, resulting in apoptosis. FoxO1 mediates cell cycle arrest via upregulation of the cell cycle inhibitors p21 and p27.

FoxO3a is a key transcription factor of apoptosis (Sakoe, Sakoe, Kirito, Ozawa, & Komatsu, 2010). FoxO3a DNA-binding elements exist in the TRAIL promoter, indicating that TRAIL is a direct target of ATRA-induced FoxO3a. TRAIL has been shown to be upregulated in human sebaceous gland cells during treatment with isotretinoin. Isotretinoin increases FoxO/TRAIL signalling in sebaceous glands of patients with acne, resulting in sebocyte apoptosis. The resulting suppression of sebum is the major anti-acne action of oral isotretinoin therapy.

An accumulating body of information suggests that the therapeutic, adverse, teratogenic and chemopreventive effects of isotretinoin are all mediated by upregulation of FOXO1 and other FOXO transcription factors. The proposed isotretinoin→ATRA→RAR→FOXO interaction offers a hypothetical insight into the mode of isotretinoin action and could explain most therapeutic, adverse and teratogenic effects of isotretinoin in the treatment of acne by a common mode of FOXO-mediated transcriptional regulation and apoptosis.

Nelson, et al., (2009) discuss the temporal changes in gene expression in patients' skin following treatment with isotretinoin that substantiate many of the clinical, histological and biochemical effects of isotretinoin and other retinoids noted in previous studies. These data, combined with recent findings regarding the effects of isotretinoin on apoptosis, cell cycle arrest and induction of neutrophil gelatinase-associated lipocalin (NGAL) expression, suggest a putative model wherein isotretinoin exerts a rapid effect in inducing apoptosis and cell cycle arrest within the sebaceous gland that is, in part, mediated by expression of NGAL. This leads to a decrease in sebaceous gland size beginning at 1 week of treatment and continuing through 8 weeks of treatment, and perhaps beyond with a subsequent decrease in the expression of genes involved in lipid production. Nelson hypothesises that after the initial induction of apoptosis and cell cycle arrest within the sebaceous gland, the skin adopts a wound healing-like pattern of gene expression and subsequently undergoes substantial repair and remodelling as shown by increased expression of extracellular matrix proteins.

It is unknown whether the effect of isotretinoin on FOX transcription factors and apoptosis is limited to the active treatment period or whether there is prolonged down-regulation of signalling in sebaceous stem cells via epigenetic changes. Any such epigenetic changes could be responsible for persistence of effects after active treatment with isotretinoin has been stopped.

### **3.1.2. Genetic Polymorphisms**

Genetic polymorphisms or mutations of components of the death-signalling ATRA-FoxO3-TRAIL cascade may explain the observed individual susceptibilities enhancing isotretinoin-mediated apoptosis.

Genetic polymorphisms in the gene RARA have been linked with an increased risk of adverse effects of isotretinoin (Alzoubi, et al., 2013). Three-locus haplotype (rs2715554 C/T - rs4890109 G/T - rs9303285 T/C) analysis showed that frequencies of CTG and TTG haplotypes are significantly associated with occurrence of arthralgia, myalgia, nosebleeds and headache in patients treated with isotretinoin. These side effects are all listed in the product information as possible side effects associated with isotretinoin.

In addition, TCG haplotype was associated with nosebleeds and headache, whereas TTT haplotype was associated with arthralgia and myalgia.

Levels of aspartate aminotransferase (AST) were increased in patients with the TC genotype of rs2715554 polymorphism, whereas the allele T of rs9303285 was found to be protective against developing depression in patients treated with isotretinoin (Alzoubi, et al., 2013).

As such, genetic variations of critical regulators of isotretinoin-induced apoptotic signalling may explain subgroups with increased risk of side effects or treatment resistance while receiving systemic isotretinoin. Melnik hypothesised that screening for gene polymorphisms that increase susceptibility for isotretinoin-induced apoptosis and isotretinoin-associated depression may be helpful to identify individuals with increased isotretinoin-mediated apoptotic signalling in the future (Melnik, 2017).

In summary, one of the main underlying mechanisms of the mode of action and adverse effects of isotretinoin is apoptosis. The magnitude of apoptotic signalling induced by isotretinoin may depend on genetic variations, such as RARA polymorphisms. The data provide further insights into the mode of action of isotretinoin, its risk profile, and may at least partly explain increased susceptibility for individual apoptosis-related adverse effects in subgroup of people with genetic variations of isotretinoin-induced apoptotic signalling pathways.

### **3.1.3. Isotretinoin, FoxO1 and the androgen receptor**

Androgen receptor (AR) mediated signal transduction plays an essential role for the stimulation of the size of sebocytes and sebum production as well as keratinocyte proliferation. Increased androgen receptor proteins have been found in the skin of patients with acne (Schmidt, Spona, & Huber, 1986), (Boudou, et al., 1995). FoxO1 represses the function of the androgen receptor. Oral isotretinoin treatment has been shown to decrease serum IGF-1 levels (Karadag, Ertugrul, Tural, & Akin, 2010) which may decrease AR-mediated gene expression. Decreased AR protein levels have been observed in skin of male patients with acne after oral isotretinoin treatment (Boudou, et al., 1995). These data imply that isotretinoin treatment may downregulate the transcriptional activity of AR by increasing the nuclear concentration of the AR co-suppressor FoxO1.

### 3.1.4. FoxO and isotretinoin mediated suppression of oxidative stress

Isotretinoin treatment in acne is considered to have beneficial effects due to its ability to suppress the formation of reactive oxygen species (ROS). The ability of neutrophils to produce ROS was significantly increased in patients with inflammatory acne. The involvement of ROS generated by neutrophils appears to play an important role in the disruption of the integrity of the follicular epithelium promoting inflammatory processes of acne. The effect of isotretinoin on the generation of ROS by stimulated human neutrophils showed that isotretinoin exerted an antioxidant activity against the superoxide anion (Melnik, 2017). One of the most important functions of FoxOs is the protection of cells from oxidative damage by increasing transcription of multiple genes regulating scavenging of ROS. FoxO1 controls the promoter activity of the key enzyme of cytochrome synthesis, haem oxygenase. Upregulated FoxO1 downregulates the synthesis of haem, the prosthetic group of haemoglobin and various cytochromes of the mitochondrial respiratory chain involved in ROS formation (Melnik, 2017). Thus, isotretinoin-induced upregulation of FoxO1 may explain the suppression of mitochondrial ROS generation and increased ROS catabolism, thereby normalising the increased ROS generation present in acne.

### 3.1.5. Isotretinoin and pituitary hormone levels in patients with acne

Several hormones affecting sebaceous gland activity have been linked to acne. These may include androgens, oestrogens, growth hormone, insulin, insulin-like growth factor 1 (IGF-1), corticotropin-releasing hormone (CRH), melanocortins such as adrenocorticotrophic hormone (ACTH) and melanocyte-stimulating hormone (MSH), and glucocorticoids (Lolis, Bowe, & Shalita, 2009). In one study by Karadag et al (2011), the authors aimed to compare the effect of low-dose, intermittent and high-dose isotretinoin regimens on hormone systems possibly related to acne pathogenesis. Various hormone systems were evaluated before and after 3 months of isotretinoin treatment in 47 patients with acne. Free triiodothyronine (T3), thyroid-stimulating hormone and thyroid-stimulating hormone receptor antibody levels decreased significantly during isotretinoin treatment ( $p < 0.001$ ,  $p < 0.02$  and  $p < 0.02$ , respectively), as did those of luteinising hormone (LH), prolactin and total testosterone ( $p < 0.005$ ), as well as morning cortisol and adrenocorticotrophic hormone ( $p < 0.005$  and  $p < 0.05$ , respectively). The study concluded that isotretinoin causes mild suppression of pituitary hormone levels, which may be beneficial for tackling the pathogenesis of acne (Karadag, Ertugrul, Tural, & Akin, 2011). Unfortunately, there was no report on whether the levels had fallen below normal and the number included in the study was too small to make results generalisable.

Another study by Karadag, et al., (2015) in 105 patients with acne showed after 3 months of treatment with isotretinoin, levels of LH ( $p < 0.001$ ), prolactin ( $p < 0.001$ ), total testosterone ( $p < 0.001$ ), ACTH ( $p < 0.001$ ), cortisol ( $p < 0.001$ ), insulin-like growth factor-binding protein 3 ( $p < 0.001$ ), IGF-1 ( $p = 0.002$ ), growth hormone ( $p = 0.002$ ) and free T3 (fT3) ( $p < 0.001$ ) had decreased significantly. The patients were divided into 3 groups; the first group received 0.5 to 1 mg/kg per day, the second 0.2 to 0.5 mg/kg per day and the third intermittent 0.5 to 1 mg/kg per day (only 1 week in 1 month) isotretinoin treatment. The authors concluded that isotretinoin affects pituitary hormones at all 3 doses. The differences in pituitary hormones are more pronounced in high-dose treatment which reflects the authorised posology for isotretinoin in the UK. The weakest effect was observed in the intermittent-dose group. By affecting the PPAR $\gamma$ /RXR system, isotretinoin may therefore affect hormone systems. These changes in various hormone systems may be related to the effectiveness of isotretinoin in treating resistant acne.

A study by Feily, et al., (2019) in 36 women, aged 18 to 30 years, with moderate-to-severe nodulocystic acne measured serum hormone levels before and after 3 months of low-dose (20mg per day) isotretinoin. Serum levels of testosterone ( $p = 0.015$ ), prolactin ( $p = 0.001$ ), and

dihydrotestosterone ( $p = 0.001$ ) were significantly decreased after isotretinoin treatment. In contrast, serum levels of dehydroepiandrosterone ( $p = 0.001$ ) significantly increased after isotretinoin treatment. LH, follicle stimulating hormone, free testosterone, and 17-hydroxyprogesterone showed no significant change after treatment ( $p > 0.05$  for all). The study concluded that isotretinoin alone could decrease androgen levels but increase an important driver of acne pathogenesis (dehydroepiandrosterone). These results are relatively concordant with those of Lookingbill, et al., (Lookingbill, Demers, Tigelaar, & Shalita, 1988) and (Karadag, et al., 2015). Lookingbill, et al., (1988) found that isotretinoin caused elevation of free testosterone and depression of dihydrotestosterone. Karadag, et al., (2011) found that isotretinoin therapy resulted in decreased prolactin and total testosterone levels but increased dehydroepiandrosterone levels. In another clinical trial, total testosterone and prolactin levels were significantly decreased in patients treated with isotretinoin, with no change in free testosterone and dehydroepiandrosterone levels (Karadag, et al., 2011).

Together, these reports suggest that isotretinoin therapy decreases total testosterone, prolactin, and dihydrotestosterone, while increasing free testosterone and dehydroepiandrosterone and that this contributes to its effect on treating severe acne. Although the mechanism of these changes is not well understood, it is hypothesised that isotretinoin induces the separation of testosterone from sex hormone-binding globulin, thereby increasing free testosterone levels and inhibiting the transformation of testosterone to dihydrotestosterone. The implications of these changes for the natural history of side effects relating to isotretinoin are not discussed in the study papers and whether the changes persist beyond treatment is unclear.

### 3.2. Mechanisms of action for side effects

While the exact mechanism of action of isotretinoin has not been fully elucidated, it has been established that isotretinoin has wide-ranging activity on a number of physiological pathways. This section discusses how these mechanisms could relate to some of the side effects observed in association with isotretinoin therapy. A review by Bodo Melnik, (2017), proposes that the pharmacological mechanism of action of isotretinoin in the treatment of severe acne, acute promyelocytic leukaemia, and neuroblastoma results from apoptosis. Furthermore, that apoptosis may be the underlying and unifying mechanism of the side effects of isotretinoin.

Apoptosis of other cells, which are also highly susceptible for isotretinoin-induced apoptosis, such as neural crest cells or neural crest-derived neuroblastoma cells and leukaemia cells, can potentially result in either therapeutic or side effects as summarised in table 1.

Table 1. Isotretinoin-induced apoptosis, potential effects and whether it is reflected in the product information (Melnik, 2017)

| Cell type            | Effect         | Information in product information   |
|----------------------|----------------|--|
| Neural crest cells   | Teratogenicity | Isotretinoin is a powerful human teratogen inducing a high frequency of severe and life-threatening birth defects. Use of isotretinoin requires a pregnancy prevention programme due to teratogenic effects. The risks are reflected in the Summary of Product Characteristics (SmPC) and Patient Information Leaflet (PIL). |
| Hippocampal neurones | Depression     | Warnings in sections 4.4 and 4.8 of the SmPC regarding the risk of depression  |

|  |  |   |
|--|--|---|
|  |  | (rare) and other psychiatric disorders. This information is reflected in the PIL.   |
| Epidermal keratinocytes and mucosa cells | Mucocutaneous side-effects                                 | Warnings in sections 4.4 and 4.8 of the SmPC regarding the risk of skin and subcutaneous tissue disorders. This information is reflected in the PIL.  |
| Hair follicle cells                      | Telogen effluvium  | Hair disorders is listed as a possible very rare side effect in section 4.8 of the SmPC. The risk of changes to hair are in the PIL.  |
| Intestinal epithelial cells              | Inflammatory bowel disease                                 | Warnings in sections 4.4 and 4.8 of the SmPC regarding the risk of gastrointestinal disorders including inflammatory bowel disease (very rare). This is reflected in the PIL.   |
| Skeletal muscle cells                    | Myalgia and release of creatine kinase                     | Warnings in sections 4.4 and 4.8 of the SmPC regarding the risk of musculo-skeletal and connective tissue disorders including myalgia (very common) and blood creatine phosphokinase increased (very rare). This information is reflected in the PIL.   |
| Hepatocytes                              | Release of transaminases and very low-density lipoproteins | Warnings in sections 4.4 and 4.8 of the SmPC regarding the risk of hepatobiliary disorders including transaminase increased (very common). High density lipoprotein decreased is also listed as a very common adverse reaction in section 4.8 of the SmPC. This information is reflected in the PIL |
| Meibomian gland                          | Dry eye  | Warnings in sections 4.4 and 4.8 of the SmPC regarding the risk of eye disorders including dry eyes (very common). This information is reflected in the PIL.  |

### 3.2.1. Mental health and cognitive effects

#### 3.2.1.1. Depression

##### 3.2.1.1.1. *Impairment of Neurogenesis*

Studies have demonstrated that the hippocampus is one of the brain regions where new neurones are formed; a phenomenon called neurogenesis (Duman, 2004) (Salposky, 2001) (Vaidya, Fernandes, & Jha, 2007) (Apple, Fonsesca, & Kokovay, 2016) (Sakai, Crandall, Brodsky, & McCaffery, 2004) (Crandall, et al., 2004) (Griffin, et al., 2010) (Hu, et al., 2016). Recent theories for the process by which depression develops suggest decreased hippocampal and prefrontal cortex neurogenesis (Duman, 2004) (Salposky, 2001) (Vaidya, et al., 2007). In particular, the addition of new neurones within the hippocampus, a limbic region implicated in mood disorders, is compromised in animal models of depression (Vaidya, et al., 2007). In contrast, antidepressant treatment seems to operate by an increase in neurogenesis, which is chronologically seen during the same period as the clinical improvement (Vaidya, et al., 2007), (Apple, et al., 2016). Another irregularity in the hippocampus associated with depression is reduction in hippocampal volume.

Abnormal retinoid levels can have neurologic effects, and retinoids are widely implicated in the development of neurobehavioural abnormalities (Adama, 2010). Beyond its prenatal effects, retinoic acid may influence cognition in adult life. RARs are expressed in the adult hippocampus, thalamus, and pons (RAR  $\alpha$ ), and the striatum, hypothalamus, and medulla (RAR  $\beta$ ), and retinoic acid has been found to modulate synaptic plasticity and neurogenesis in adulthood (Duman, 2004). Isotretinoin is hypothesised to induce depression-related behaviours by decreasing adult neurogenesis or altering expression of components of the serotonergic neurotransmitter system, resulting in impaired serotonin signalling (Apple, et al., 2016). An association of retinoic acid signalling with stress and depression is supported by the overlap between brain areas implicated in both (Lynburg, et al., 1990). Furthermore, functional brain imaging has revealed a decrease in brain metabolism in the orbitofrontal cortex (an area established to mediate symptoms of depression) in patients with acne treated with isotretinoin. Brain functioning in adults was measured before and after 4 months of treatment with isotretinoin. Isotretinoin but not antibiotics was associated with decreased brain metabolism in the orbitofrontal cortex ( $-21\%$  change versus  $2\%$  change for antibiotics) (Bremner, 2005).

Upregulation of FOXO1 by isotretinoin may inhibit hippocampal neurogenesis by encouraging apoptosis (Crandall, et al., 2004). FoxO1 is strongly expressed in the striatum and neuronal subsets of the hippocampus (in other words the dentate gyrus and the ventral/posterior part of the cornu ammonis regions). Upregulation of hippocampal FoxO1 levels may inhibit hippocampal neurogenesis and may thus be responsible for the adverse psychiatric drug effects in some disposed individuals. Isotretinoin-induced apoptotic effects on hypothalamic cells may have downstream regulatory effects on the pituitary. Thus, a decrease in ACTH and other pituitary hormones may be expected during isotretinoin treatment.

This is demonstrated in [Figure 7 of the scientific hypothesis paper by Melnik \(2011\)](#), which shows mechanisms for isotretinoin's effect on the central nervous system mediated by FoxO1 upregulation.

A study by O'Reilly, et al., (2006) showed that chronic administration of 13-cis-RA leads to depression-related behaviours in mice. Young, adult male mice received 13-cis-RA (1 mg/kg) by daily intraperitoneal injection for 6 weeks. This treatment paradigm produced plasma levels of 13-cis-RA in the mice that are comparable to those reported in human patients taking oral isotretinoin. In both the forced swim test and the tail suspension test, it was found that 13-cis-RA-treated mice spent significantly more time immobile compared to vehicle-treated controls. Taken together, these results suggest that administration of 13-cis-RA increases depression-related behaviours in mice. Isotretinoin treatment of mice results in both decreased hippocampal neurogenesis and reduction in hippocampal volume (Sakai, et al., 2004), (Crandall, et al., 2004). Treatment of hypothalamic cells with  $10\ \mu\text{M}$  isotretinoin for 48 hours decreased cell growth to  $45.6 \pm 13\%$  of control (Griffin, et al., 2010). Griffin, et al., hypothesised that the ability of isotretinoin to decrease hypothalamic cell numbers may contribute to the increased depression-related behaviours observed in mice.

A study by Hu, et al., (2016) confirmed that intracerebroventricularly applied ATRA to adult rats increased RAR $\alpha$  protein expression in the hippocampus, suggesting an activation of ATRA-induced signalling mechanisms. In these rats, ATRA-induced impairments in hippocampal neurogenesis correlated with depression-like symptoms. Remarkably, retinoic acid-inducible gene 1 (RAI-1), which increases during neuronal differentiation, was found to be significantly upregulated in brains from patients with schizophrenia, bipolar disorder, or major depression (Haybaeck, et al., 2015) (McCaffery & Drager, 1994). Therefore it was hypothesised that isotretinoin-mediated suppression of hippocampal neurogenesis could provide a plausible biological mechanism explaining depressogenic effects of the drug. Individuals with pre-existing impairments of hypothalamic neurogenesis may be at higher risk for the development of isotretinoin-augmented depression.

#### 3.2.1.1.2. *Dopamine Systems*

Another plausible biological mechanism underlying the proposed causative relationship between isotretinoin and depression is the effect of retinoids on brain dopamine systems (McCaffery & Drager, 1994) (Samad, Krezel, Chambon, & Borrelli, 1997). This has been suggested, although remains speculative. Etretinate, another retinoid used as therapy in cutaneous disease, has been linked in case reports with depression (McGuire & Lawson, 1987). Additionally, it has been suggested that hypervitaminosis A is associated with psychiatric symptoms including depression, and hypervitaminosis A syndrome has been proposed as a paradigm of retinoid side effects (Silverman, Ellis, & Voorhees, 1987).

#### 3.2.1.1.3. *Genetic Polymorphisms*

The effect of genetic polymorphisms (variations) of the RARA gene has been investigated for the relationship with depression. In a study of 300 patients treated with oral isotretinoin, it was shown that the T allele of rs9303285 was protective against developing depression and the polymorphisms rs2715554 and rs54890109 were not associated with developing depressive symptoms during use of isotretinoin (Alzoubi, et al., 2013). However, this study requires further validation to assess the possible associations and explore whether other, as yet unidentified, factors have a role in the clinical outcome for oral isotretinoin. There is currently no commercially available test to use for screening for these polymorphisms.

#### 3.2.1.1.4. *Biotin*

Isotretinoin administration has also been shown to affect metabolic pathways, alterations of which have been linked to depression; two examples involve biotin and homocysteine. Biotin, a member of the B vitamin family (vitamin B-7) is a required nutrient that is involved in the biosynthesis of fatty acids, gluconeogenesis, and metabolism of amino acids. Side effects of biotin deficiency include hair loss, conjunctivitis, neuromuscular dysfunction, skin changes, neurological dysfunction, and depression (Charles, et al., 1979) (Sweetman, Surh, Baker, & Nyhan, 1981) (Scott, 1958) (Sydenstricker, Singal, Briggs, DeVaughn, & Isbel, 1942) (Baugh, Malone, & Butterworth, 1968) (Levenson, 1983) (McMahon, 2002) (Charles, et al., 1979) (Schulpis, Georgala, Papkonstantinou, Michas, & Karikas, 1999). These effects are currently listed as possible side effects of isotretinoin.

For instance, Baugh described a dietary-induced case of biotin deficiency resulting in anorexia, nausea, vomiting, glossitis, skin changes and depression while Levenson (1983) described a biotin deficiency case which was associated with depression and thoughts of suicide. These symptoms went away after biotin supplementation. One mechanism by which biotin is recycled in the body, maintaining its availability, is supported by the enzyme biotinidase (Schulpis, et al., 1999). Mutations in this enzyme result in biotin deficiency (Bremner, et al., 2005), (Csoka & Szyf, 2009). Isotretinoin administration to humans is associated with a decrease of biotinidase (Ding, Kam, Dieckow, & Sullivan, 2013), and the presumed decrease in biotin that would result from this may contribute to depression.

#### 3.2.1.1.5. *Homocysteine*

Homocysteine is a sulphur containing amino acid that is involved in carbon transfer reactions. Homocysteine can receive a methyl group from 5'-methyltetrahydrofolate and become re-methylated to methionine, the immediate precursor of S-adenosylmethionine (SAM), a donor of methylation reactions involved in the synthesis of DNA, proteins, phospholipids, neurotransmitters and polyamines. SAM is involved in the synthesis in the brain of dopamine, norepinephrine and

serotonin; neurotransmitters that have been linked to depression. Many studies have found a relationship between elevated homocysteine levels, lower folate concentrations, and depression (Schulpis, Karikas, Georgala, Michas, & Tsakiris, 2001). Isotretinoin administration to humans was shown to be associated with increased concentrations of homocysteine, as well as decreases in 5-methyl-tetrahydrofolate (Bremner, 2012) providing a potential metabolic mechanism by which isotretinoin may promote depression (Bressa, 1994), (Almeida, et al., 2005), (Reynolds, Carney, & Toone, 1984).

#### 3.2.1.1.6. *Brain metabolism*

The influence of isotretinoin on brain metabolism has been directly investigated using positron emission tomography (PET) with fluorodeoxyglucose (FDG), a technique that maps regional differences in glucose uptake in the brain. A total of 28 people with acne were imaged before and after 4 months treatment with 13-cis retinoic acid or antibiotics (13 with 13-cis RA, 15 with antibiotics). Patients were also assessed for depression using the Hamilton Depression Scale (Ham-D). This study revealed that 4 months of 13-cis retinoic acid treatment led to a significant reduction in brain metabolism in the orbitofrontal cortex (Bremner, et al., 2005) a region that has been associated with depression. This is demonstrated in [figure 3 in the paper by Bremner and colleagues \(2005\)](#), which shows a visible decrease in metabolism in the orbitofrontal cortex in a representative patient receiving isotretinoin treatment for acne.

In the case of patients reported to the Norwegian Medicines Agency, single photon emission computed tomography (SPECT) of the brain was performed in 15 cases who reported lasting neurological symptoms. Abnormal brain function was seen in all cases involving altered or reduced frontal lobe blood flow (Bremner, et al., 2005). Ten of these patients were evaluated to have organic brain damage. This study was funded by an isotretinoin campaign group and was considered by an Expert Working Group of the CHM in 2005.

#### 3.2.1.2. Psychosis

There is very little information about the mechanism behind the reported association between isotretinoin use and psychosis. Goodman described three lines of evidence suggesting that retinoids may be implicated in the pathogenesis of schizophrenia (Scott, 1958). First, several manifestations similar to those caused by retinoid signalling dysfunction are found in patients with schizophrenia and their relatives. These manifestations include thought disorder, enlarged ventricles, agenesis of the corpus callosum and microcephaly. The second line of evidence implicating retinoids in the genetic aetiology of schizophrenia is the occurrence of known genetic markers in schizophrenia (candidate susceptibility genes), which happen to be loci of retinoid pathways or metabolic cascades (such as 6p22, 22q12-13). Finally, the transcriptional activation of dopamine D2 receptor and other schizophrenia candidate genes, such as the glutamate receptors, is regulated by retinoic acid. In a more recent work by Rioux and Arnold (2005) it was reported that the expression of retinoic acid receptor  $\alpha$  is increased two-fold in the granule cells of the dentate gyrus in schizophrenia. The authors concluded that the evidence provided supports the hypothesis that retinoid pathway dysregulation may be a factor in the aetiology of the disease.

### 3.2.2. **Sexual function and fertility**

#### 3.2.2.1. Sexual dysfunction

Biological mechanisms by which isotretinoin could cause sexual dysfunction are theoretical and include a reduction in plasma testosterone levels. However, it is not clear from available studies



whether the reduction in testosterone with use of isotretinoin results in levels below the normal range, since normal ranges are age dependent and the data are lacking. In addition, the results for the different androgens are conflicting. No data on the role of isotretinoin induced apoptosis of cells in or innervating the reproductive tract were identified.

There is some evidence for an effect of isotretinoin on male hormone receptors but the data are restricted to a study in 6 male patients (Boudou, et al., 1995). An oral daily dose (mean +/- SD, 0.75 +/- 0.05 mg/kg) of isotretinoin was administered for 3 months to 6 male patients with acne. The therapy resulted in complete resolution of acne in 4 patients and improved acne significantly (score 1) in 2 patients. No change in serum testosterone was observed but significant decreases in 5 alpha-dihydrotestosterone, 5 alpha-androstane-3 alpha,17 beta-diol glucosiduronate, and androsterone glucosiduronate levels were found after treatment.

Androgen receptor status was investigated in back skin biopsies obtained in acne areas before and after 3 months of isotretinoin treatment. The treatment did not modify the binding affinity constant of skin androgen receptor (0.44 vs. 0.32 nmol/L), but it did induce a 2.6-fold decrease in its binding capacity. These data clearly showed that the skin androgen receptor was sensitive to oral isotretinoin administration in patients with acne. The decrease in skin androgen receptor levels (Boudou, et al., 1995) and the reported suppression of skin 5 alpha-dihydrotestosterone production by isotretinoin treatment (Boudou, et al., 1994) appeared consistent with the involvement of androgen receptor and 5 alpha-dihydrotestosterone in the pathogenesis of acne. Sebum production is under androgen control, and an abnormal response of the pilosebaceous unit to androgens appears to be implicated in the pathogenesis of acne. The impact of the findings on male hormone receptors for sexual dysfunction is unknown.

In a letter to the editor of the Lancet in 1994, (Coleman & MacDonald, 1994) a dermatologist reported sexual dysfunction in a 29-year-old male patient on isotretinoin and discussed possible mechanisms relating to the drug in the absence of obvious neurological dysfunction. In this case the patient recovered after stopping isotretinoin treatment. The effect of isotretinoin on the goblet cells of the seminal vesicles responsible for seminal fluid production resulting in absent ejaculation was described as a possible mechanism but further study has not confirmed this mechanism (McMahon, 2002).

#### 3.2.2.2. Fertility

The current isotretinoin SmPC states that isotretinoin, in therapeutic dosages, does not affect the number, motility and morphology of sperm and does not jeopardise the formation and development of the embryo as a consequence of a man taking isotretinoin; there is no information about female fertility in the product information.

The Yellow Card scheme has received the following reports of suspected side effects relating to possible fertility concerns; semen analysis abnormal (3 cases), sperm volume decreased (1 case) and sperm concentration decreased (1 case).

##### 3.2.2.2.1. *Male fertility*

A study in 2016 (Cinar L. , et al., 2016) found no adverse effects of oral isotretinoin in patients with acne on male fertility, given a total dose of 120 mg/kg over a period of 6 months. The study included 81 male patients, who were older than 18 years of age, and had severe or refractory acne vulgaris. They were given a total dose of 120 mg/kg of systemic isotretinoin over a period of 6 months. Before and after the study, the spermiogram parameters of the patients were evaluated to show any possible effect on male fertility. The patients' total testosterone, follicle stimulating hormone and

luteinising hormone levels were also evaluated. All of the spermiogram parameters changed positively ( $p < 0.05$ ). There was no significant change in the hormone levels. In one study by Amory et al, it was demonstrated that in 19 men with infertility due to low sperm counts, isotretinoin improved sperm counts, resulting in 6 pregnancies and 5 live births (Moy, McNamara, & Lin, 2015).

Animal studies have demonstrated impaired spermatogenesis. In adult male gerbils, isotretinoin induced almost complete cessation of spermatogenesis and produced alterations in the cytoplasm of Leydig cells (Sadek & Abdul-Mohsen, 1999). In the adult lizard administration of ATRA impaired spermatogenesis and enhanced testicular germ cell apoptosis (Comitato, Esposito, Cerbo, Angelini, & Varriale, 2006). These studies point to an increased risk of isotretinoin-induced germ cell apoptosis in these retinoid-susceptible species but the implication for humans is unknown.

#### 3.2.2.2.2. *Female fertility*

In humans, a study was conducted to investigate possible effects of isotretinoin on female fertility by measuring ovarian reserve. Serum anti-Mullerian hormone (AMH) levels were measured at the beginning and at the end of isotretinoin treatment in 22 patients with acne and in 22 women without acne. The mean AMH level before treatment was 5.77 ng/mL in the study group and 3.79 ng/mL in the control group ( $p=0.008$ ). Following treatment, the mean AMH level was 4.69 ng/mL in the study group. This mean AMH level after treatment was statistically lower than the AMH level before treatment ( $p=0.012$ ). There was no significant difference between the mean AMH level at the end of treatment and that of the control group ( $p=0.20$ ). The high level of pre-treatment AMH levels could be evidence of hyperandrogenism in women with acne, even if they are not identified as having polycystic ovary syndrome (PCOS) or hyperandrogenism. Decrease in AMH levels following exposure to isotretinoin may suggest that it has a detrimental effect on the ovaries (Kamm, 1982).

However, Cinar, et al., (2017) excluded long-term adverse effects on markers of female fertility of systemic treatment with isotretinoin in 79 patients. At 12 months after the end of systemic isotretinoin treatment, patients were re-evaluated by using the same parameters, which include AMH, ovarian volume (OV), antral follicle count (AFC), follicle-stimulating hormone (FSH), LH, estradiol, free testosterone and total testosterone. The changes in the mean AMH, OV and AFC were statistically significant between the sixth and eighteenth months (the end of systemic isotretinoin treatment and 12 months treatment free). The mean AMH, OV and AFC values at the beginning and at the eighteenth month were statistically similar.

Animal studies show species-specific adverse effects of isotretinoin. Abali, et al., (2013) conducted a study about the effect of isotretinoin on ovarian reserve in female Sprague-Dawley rats, which showed a deteriorative ovarian reserve. Notably, the number of ovarian follicles with apoptotic granulosa cells was increased in the experimental groups receiving isotretinoin. The implications for humans are uncertain.

### 3.3. Discussion

Retinoids are recognised to play a critical role in normal embryonic development and the control of cellular growth, differentiation and apoptosis. Isotretinoin, the 13-cis isomer of retinoic acid, acts as a pro-drug that is converted intracellularly to metabolites that are agonists for RAR and RXR nuclear receptors which regulate transcription of a variety of genes and signalling pathways. It is theorised that differences in receptor polymorphisms may underlie the differences in both therapeutic and adverse effects experienced by patients taking isotretinoin. These polymorphisms are yet to be identified for routine use in clinical practice.

Isotretinoin is isomerised to ATRA and it is ATRA that binds to the retinoic acid receptor leading to the cascade involving activation of the FoxO proteins, TRAIL and caspases, ultimately resulting in apoptosis of not just target sebocytes but a variety of other cells, which may account for the wide range of potential side effects associated with isotretinoin. It is not clear from the available data whether the effects on the apoptosis cascade persist once isotretinoin is removed or if this mechanism can explain the reported continuance of some side effects beyond the treatment period through an epigenetic effect.

Isotretinoin achieves efficacy in acne treatment by influencing sebocyte cell-cycle progression, cellular differentiation, cell survival and apoptosis as well as the hormones in the hypothalamo–pituitary axis. There is compelling evidence that the major mode of therapeutic action is sebocyte apoptosis via effects on FOX transcription factors. FOXO also play a pivotal role in the regulation of androgen receptor transactivation, as well as several other receptors implicated in the pathogenesis of acne. An accumulating body of evidence suggests that the therapeutic, adverse, and teratogenic effects of isotretinoin may all be mediated by upregulation of FOXO-mediated gene transcription.

The impact of isotretinoin on the androgens implicated in acne pathogenesis is less clear. There is some evidence for an impact on the expression and function of androgen receptors (Boudou, et al., 1995). The results of 3 studies looking at the impact of isotretinoin on male hormones implicated in the pathogenesis of acne show a reduction in total testosterone but it is not clear if this reduction is below normal values. The study by Karadag et al in 2011 showed a decrease in other androgens but an increase in dehydroepiandrosterone - an important driver of acne after isotretinoin treatment. One study by Lookingbill, et al., in 1988 showed an elevation of free testosterone and a reduction in dihydrotestosterone.

A reduction in testosterone has been postulated to be a potential mechanism underlying the occurrence of sexual side effects reported in association with isotretinoin but the data are unclear and further studies to confirm or refute the association are required. There are no data on the apoptotic effects of isotretinoin on the genital tract or the nerves that innervate the organs of reproduction. Effects on human fertility show no overall harmful effects (Cinar S. L., et al., 2017), (Akturk, et al., 2014). Some animal studies (Abali, et al., 2013), (Sadek & Abdul-Mohsen, 1999), (Comitato, et al., 2006) show a species-specific adverse effect on male and female fertility; the implication for humans is currently uncertain.

Studies have demonstrated that the hippocampus is one of the brain regions where new neurones are formed; a phenomenon called neurogenesis (Vaidya, et al., 2007), (Apple, et al., 2016), (Hu, et al., 2016). Recent theories for the pathogenesis of depression suggest decreased hippocampal and prefrontal cortex neurogenesis. In particular, the addition of new neurones within the hippocampus (a limbic region implicated in mood disorders) is compromised in animal models of depression (Vaidya, et al., 2007). In contrast, antidepressant treatment seems to operate by an increase in neurogenesis, which is chronologically seen during the same period as the clinical improvement (Vaidya, et al., 2007), (Apple, et al., 2016).

There are 4 main mechanisms identified by which isotretinoin can theoretically lead to depression. These mechanisms relate to apoptosis of hippocampal cells by upregulation of FoxO1 by isotretinoin (Crandall, et al., 2004), alterations in the serotonergic signalling system (Apple, et al., 2016), effects on the dopamine system (McCaffery & Drager, 1994), (Samad, et al., 1997) and impact on the hypothalamo–pituitary axis (Melnik, 2011).

It is postulated that individuals with pre-existing impairments of neurogenesis may be at higher risk for isotretinoin augmented depression although it is currently not possible to identify such individuals. The effect of genetic polymorphisms (variations) of the RARA gene has been investigated

for the relationship with depression (Alzoubi, et al., 2013). However, this requires further validation to assess the possible associations and explore whether other as yet unidentified factors have a role in the clinical outcome for oral isotretinoin. There is currently no commercially available test to screen for these polymorphisms.

The data available on the underlying mechanism for the relationship between isotretinoin use and psychosis are very limited. The retinoic acid-inducible gene 1 (RAI-1), which increases during neuronal differentiation, was found to be significantly upregulated in brains from patients with schizophrenia, bipolar disorder, or major depression in the study by Haybaeck in 2015.

The SmPC has a statement at the beginning of section 4.8 that mentions some of the side effects associated with the use of isotretinoin are dose-related. The side effects are generally reversible after altering the dose or discontinuation of treatment; however, some may persist after treatment has stopped.

Teratogenic effects of isotretinoin are complex but are broadly thought to relate to the apoptosis of neural crest cells. The anti-cancer effects of the retinoids seem to relate to inducing gene expression and apoptosis in cancer cells which clearly resemble the transcriptional activity of FoxO proteins. This induces malignant cells to overcome differentiation inhibition and to enter apoptotic pathways.

## **4. PSYCHIATRIC SIDE EFFECTS**

This chapter summarises the information on psychiatric side effects associated with isotretinoin considered by the Isotretinoin EWG. The Isotretinoin EWG considered data from literature and spontaneous reports and information provided by stakeholders.

The Isotretinoin EWG was asked to consider whether further regulatory action was required to minimise the risk of psychiatric disorders suspected to be associated with isotretinoin and whether further research was required to better characterise the risk of psychiatric disorders suspected to be associated with isotretinoin and to evaluate the long term impact on patients.

### **4.1. Summary of information from stakeholders provided in the call for Information**

The feedback received from the call for information described important factors associated with the demographics of respondents, the side effects they have experienced which were suspected to be associated with isotretinoin, attitudes to those experiences and knowledge of isotretinoin and how isotretinoin is used in practice. This provided a wider range of views than the examined Yellow Card data, which provided information on side effects alone.

Of the 659 completed responses received for the call for information which expressed a view, 50% communicated only positive views; 31% communicated only negative views and 19% communicated both positive and negative views or other views.

Of the 659 responses received, 427 (65%) provided information on psychiatric disorders. 45% of which were positive views, 36% were negative views and 19% expressed both positive and negative views or other views.

68% of responders expressing views on psychiatric disorders felt that additional measures were needed to optimise the safe use of isotretinoin and raise awareness of the potential risks and the remaining 32% felt no additional measures were required.

Below is a breakdown of how responders identified themselves:

- 68% as an individual who has received treatment with isotretinoin
- 20% as a family member or friend of someone who has received treatment with isotretinoin
- 18% as a healthcare professional who treated individuals with isotretinoin
- 8% as a healthcare professional who treated individuals who experienced side effects suspected to be related to isotretinoin
- 2% as researcher or academic organisation
- 2% as a healthcare organisation
- 1% as charity or patient organisation.

These figures total over 100% as responders could select multiple categories that represented them.

Information received from both the structured survey and any associated attachments have been considered in this summary.

A number of themes emerged around the positive experiences individuals, families and friends had relating to isotretinoin. These included:

- successful treatment with isotretinoin and acne resolution
- positive opinion despite unsuccessful treatment
- positive views but experienced side effects
- improved self-esteem and improvement in acne-induced mood disorders
- successful treatment in individuals with pre-existing mental health disorders
- risk communication

*'it saved my life. There was more chance of me killing myself with how my acne made me feel every day of my life than taking the medication. Disfiguring acne is unsightly and incredibly painful and has a huge enormous impact on mental wellbeing. I am so so pleased that I took isotretinoin, I just wish I had done it sooner.'*

*Comment received through call for information*

However, even with positive views expressed, many responders said that they felt additional measures are needed, mainly in the form of additional information on side effects and more comprehensive and systematic screening, monitoring and follow up of psychiatric disorders.

Patients who have experienced overwhelmingly positive physical (acne resolution) and mental health (self-esteem) improvements following acne treatment expressed worry about the potential for banning isotretinoin and the negative impact this would have on future patients.

While many of those who had positive experiences with isotretinoin were happy with their care, a significant number still proposed that additional measures may be beneficial to support patients and families to make informed decisions about treatment.

Responders citing negative experiences with isotretinoin mostly fell into the category of individuals who received isotretinoin treatment and the family/friends of individuals who have

*'I wish there were more reliable sources available to research and check potential risks as the conversations I have with my dermatologist are only monthly and are over the phone, so it is difficult to cover all potential risks that may or may not be due to Roaccutane.'*

*'Isotretinoin is incredibly effective so I think the risks can be worth it, but patients need to be more informed about the risks, as should their families be and monitoring should be closer.'*

*Comment received through call for information*

*'Nothing else is strong enough to work. If this is removed from approved acne treatments then there needs to be something just as effective to replace it before it is removed from the market as people could turn to buying it online from unapproved and unsafe websites where outcomes could be more detrimental.'*

*Comment received through call for information*

received isotretinoin treatment.

Negative experiences ranged from those who experienced psychiatric effects alone or experienced psychiatric side effects in combination with sexual disorders or other side effects.

A number of themes emerged relating to the negative experiences expressed.

These include:

- occurrence of significant and sometimes fatal psychiatric side effects considered to be attributed to isotretinoin
- continuation of side effects suspected to be associated with isotretinoin after treatment completion/discontinuation
- risk of treating one condition but developing a more debilitating condition as a result of isotretinoin treatment
- lack of clear risk communication from healthcare professionals

- poor information provision for family and friends on signs and symptoms of psychiatric side effects
- unstructured and arbitrary screening, monitoring and follow-up of patients for psychiatric conditions
- overemphasis on pregnancy prevention programme at the expense of psychiatric side effect monitoring
- prescribing for milder forms of acne (outside the licence)
- use at doses outside those recommended in the SmPC
- additional measures required for the safe use of isotretinoin
- more consideration should be given to treatment options, beyond isotretinoin, by dermatologists.

*'If a Dr tells you a drug is great... you believe them... so you get it from the pharmacy.... and the leaflet lists some side effects that you would not want. but you've already paid for the prescription and you can't call the Dr because an appointment takes months... you are just going to listen to the Dr I was never informed of how bad the reactions for this drug was and how lasting they are even though I stopped taking it. Unfortunately, when they said the symptoms wouldn't be too bad, I believed him.'*

*Comment received through call for information*

*'In our case, the PIL was not included in the packets of medication. These were dispensed by the hospital in plain white boxes with the correct number of tablets cut off and inserted. Those boxes did not contain a PIL.'*

*Comment received through call for information*

*'I believe that thorough mental health checks should be carried out before and during treatment. I was simply asked before treatment if there was any history of mental health issues in my family. No attempt to work out how my mental health was attempted. I wish I was asked to fill out questionnaires covering all parts of my mental health which were likely to be affected, and someone could have decided whether I was well enough for the treatment.'*

*Comment received through call for information*

*'I was prescribed it by a hospital dermatologist who gave me the information booklet. There was a lot of emphasis on pregnancy risk and not much on side effects. For me personally, I would have liked to have been able to discuss my side effects.'*

*Comment received through call for information*

*'In my view this medication should only be given to people suffering with severe scar forming acne. Seeing people with mild forms of acne given this medication makes me sick. It's not worth the risk.'*

*Comment received through call for information*

*'I believe that dermatologists should seek out to educate patients on skin care rather than medication for the treatment of acne- An individual who has received treatment with isotretinoin.'*

*Comment received through call for information*

## **4.2. Yellow Card Reports**

A review of the Yellow Card database of spontaneously reported suspected adverse drug reactions was undertaken to identify reports of psychiatric side effects suspected to be associated with isotretinoin between 1983 and 20 May 2021. A cumulative total of 2,987 yellow card reports detailing 7,267 reactions were identified for isotretinoin overall. Of these reports, there were a total of 806 Yellow Cards for isotretinoin that included one or more terms pertaining to psychiatric side effects.

The ten most frequently reported psychiatric side effects at the preferred term <sup>21</sup>(PT) level suspected to be associated with isotretinoin in the UK Yellow Card dataset are depression (378) suicidal ideation (136 cases), anxiety (118 cases), death by suicide (83 cases), depressed mood (75 cases), suicide attempt (59 cases), mood swings (52 cases), psychotic disorder (43 cases), aggression (42 cases) and mood altered (35 cases)<sup>22</sup>. These are all listed reactions or covered by the current warnings and precautions in the product information or both.

### **4.2.1. Age and gender**

In 60% of the reports the patient was identified as male and in 37% as female; the remainder did not report gender. The age of the patients suspected to have experienced psychiatric side effects reflects the expected age group for patients with acne. Mean age for patients reporting psychiatric side effects with isotretinoin (where reported) is 15.3 years, range 12 to 60 years. Male patients aged 11–18 years followed by male patients aged 19–24 represent the groups reporting the highest numbers of psychiatric side effects.

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<sup>21</sup> The Medical Dictionary for Regulatory Activities (MedDRA), which is the internationally agreed list of terms used for Medicines Regulation. MedDRA groups related adverse drug reaction terms in a hierarchical structure.

<sup>22</sup> It is important to note that Yellow Card reports may include multiple related side effects and so the number of cases for each reaction cannot be simply added to calculate the number of patients involved. It is also important to consider under-reporting, not all suspected side effects that occur are reported through the Yellow Card scheme.



Figure 1. Breakdown of ADR reports by age and gender

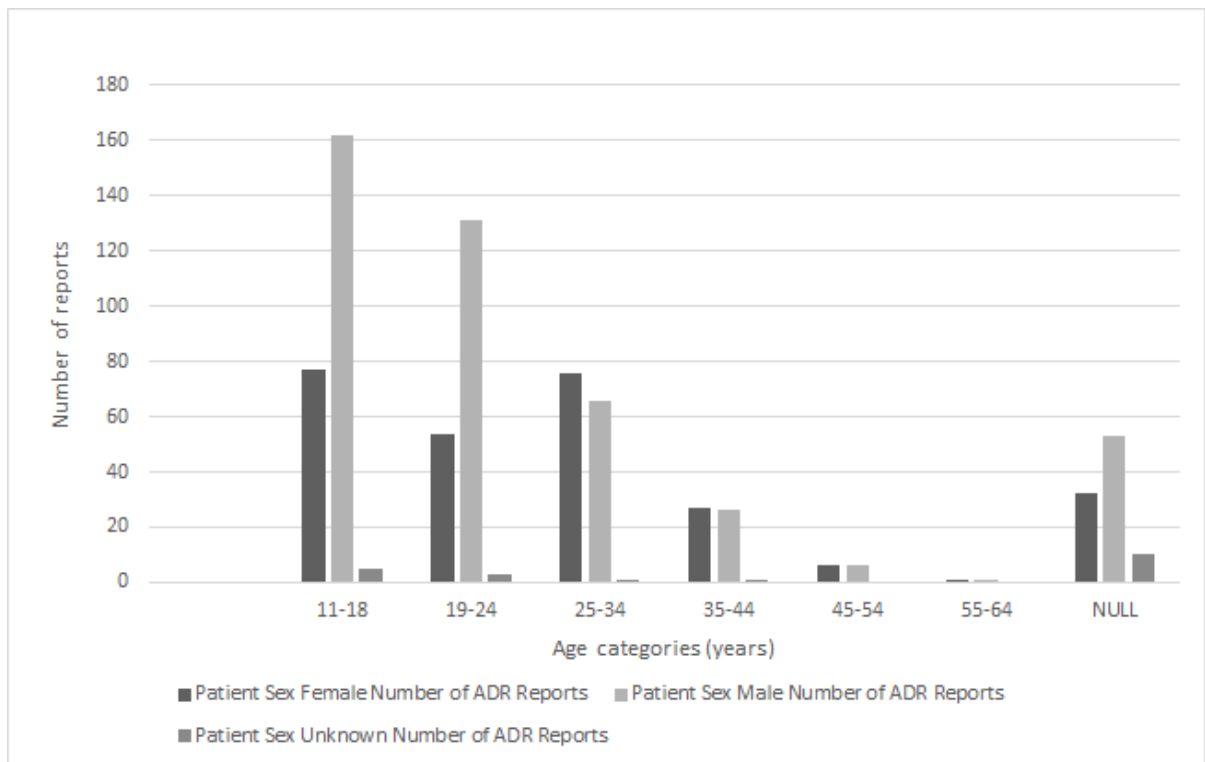
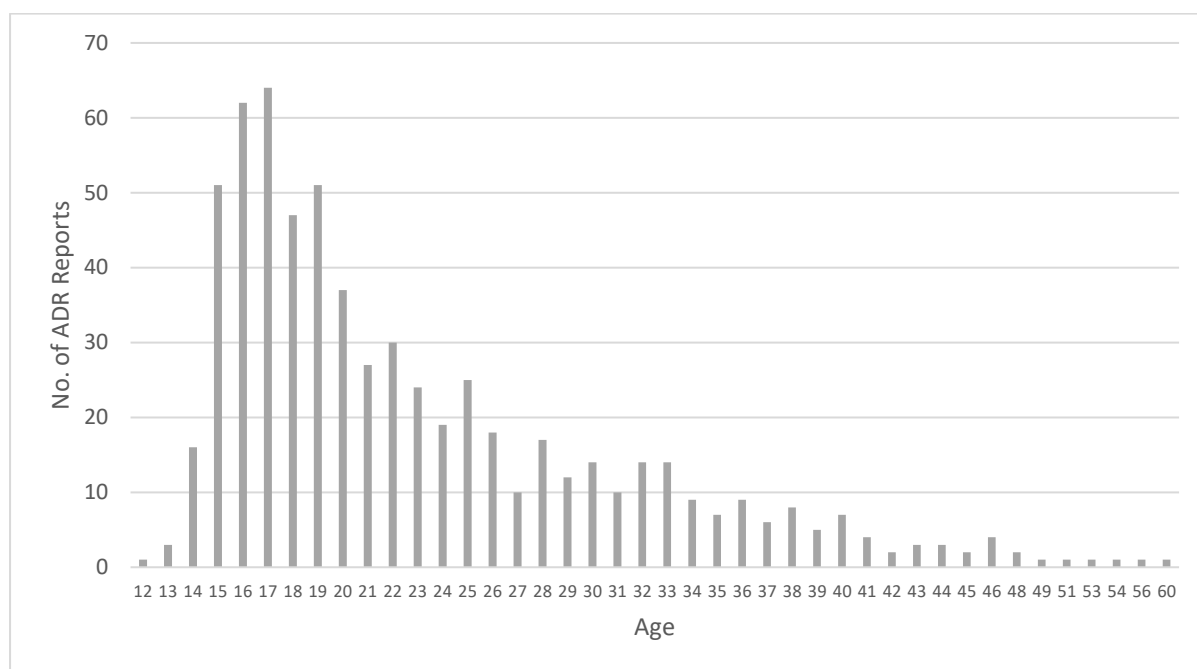


Figure 2. Breakdown of Psychiatric ADR reports by patient age



#### 4.2.2. Dose

It remains difficult to identify a relationship between psychiatric reactions considered attributed to isotretinoin and dose of isotretinoin due to a number of factors. In the Yellow Card reports, dose has not always been reported and where it has, it has been presented in a variety of different forms, for example initial dose, range of doses where a change occurred, or total dose for the course of treatment. Many patients start on a lower dose and then increase to a higher dose as recommended in the posology section of the SmPC. It is rarely possible to identify the dose the patient was taking at the time of the events, especially where they continued their therapy despite the events.

#### 4.2.3. Confounders

The majority of patients had no information provided on co-morbidities or concomitant medications, but given their generally young age, this was most likely due to the absence of these confounders.

Where concomitant medications were listed, these were primarily hormonal contraceptives, antibiotics, antidepressants, antipsychotics and topical acne treatments. For the antidepressants and antipsychotics, in most of these cases it is difficult to establish if these treatments were initiated prior to isotretinoin or were commenced to treat the adverse neuropsychiatric events experienced. As many of the cases are historical cases it is often difficult to establish the sequence of events.

#### 4.2.4. Time to event

The fact that some cases took a longer time to present needs to be considered in the context that many individuals were adolescents at the time of isotretinoin therapy. It is possible they were not fully aware of the extent of the issues when they first occurred or how to identify and raise issues of mood changes, as was noted by many responders in the call for information.

Given that isotretinoin is generally prescribed and monitored in specialist clinics, it is also possible that some events were only reported at the time of follow up appointments, and not when the event

first occurred. As events like suicidal ideation, self-injurious behaviours and depression are sensitive issues, they may not have volunteered this information without direct questioning.

The following should be taken into account when interpreting the time to event information from the Yellow Card data:

- Time for the patient to notice and appreciate the adverse effect
- Time to report the adverse event to anyone including HCPs

#### 4.2.5. Types of psychiatric side effects reported

##### 4.2.5.1. Depression

Depression is the most common psychiatric side effect reported in association with the use of isotretinoin (378 cases). In order to capture all potential cases of depression, the search was expanded and cases of depression were retrieved according to the Standardised MedDRA Query (SMQ) for Depression (excluding suicide and self-injury). This includes preferred terms related to depression or depression-related symptoms, for example depressed or altered mood, feelings of guilt or despair. There was a total of 516 UK cases in the depression SMQ at the data lock point of 20 May 2021.

*'The side effects in the long run have not been worth it, or at the very least I wish I had taken them after my education was over as the depression alone has stuck but also caused damage to my ability to operate in that environment and snowballed - going from B onwards student to barely being able to focus, concentrate on my studies.'*

*Comment received through call for information*

24% of women and 13% of men in England are diagnosed with depression in their lifetime<sup>23</sup>, and depression often occurs with other mental health issues. The Yellow Card data for depression with isotretinoin shows male patients more commonly reporting depression in association with isotretinoin than female patients.

Depression occurs in 2.1% of young people aged 5 to 19 years. In 2017, 2.7% of 11–16 year olds and 4.8% of 17 to 19 year olds met clinical criteria for depression (Crow & Eckert, 2016). This aligns closely with the age distribution for depression with isotretinoin events in the Yellow Card dataset, where 95 cases present in the age group 11-16 and 116 cases present in the 17-19 age group.

##### 4.2.5.2. Anxiety disorders

Anxiety disorders are the third most frequently reported psychiatric side effects suspected to be associated with isotretinoin treatment. There was a total of 164 UK cases of clinically relevant terms in the anxiety disorders High Level Group Term (HLGT) at the data lock point of 20 May 2021.

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<sup>23</sup> [Search - Beat \(beateatingdisorders.org.uk\)](https://www.beateatingdisorders.org.uk)

*'It began with anxiety which led to a diagnosis and treatment for OCD and it ultimately led to severe depression (including suicidal tendencies). At 14/15 I was not aware exactly what I was getting into, and the permanent debilitating side effects that would result...all patients despite age, and not just parents, should be openly counselled on the risks and potential for long term effects beyond treatment.'*

*Comment received through call for information*

There were 8.2 million cases of anxiety in the UK in 2013. Women are twice as likely to be diagnosed with anxiety (Sweeting, et al., 2015) (Wood, et al., 2019). In children, 7.2% of 5 to 19 years old experience an anxiety condition<sup>24</sup>. In 2017, 7.5% of 11 to 16 years old and 13.1% of 17 to 19 years old had an anxiety condition (Crow & Eckert, 2016). Gender distribution for anxiety disorders within the Yellow Card dataset for isotretinoin deviates from expected, with 60% of cases being in male patients. There were 23 cases in the 11 to 16 years old age group, 32 cases in the 17 to 19 age group and 88 cases age 20 and over. This is generally in line with the

expected age distribution of anxiety disorders in the background population.

Literature reports and accounts from healthcare professionals in the call for information have highlighted that emergence of anxiety is more often seen in clinical practice than depression and that their concerns are predominantly centred around isotretinoin-induced anxiety, with isotretinoin more commonly being discontinued for anxiety than depression (Salmon, Affleck, Nicolson, & Stewart, 2019). Anxiety is listed as a rare side effect ( $\geq 1/10,000$  to  $< 1/1,000$ ) and is included in the 'Psychiatric disorders' - warnings and precaution statement in the product information. This is consistent with the cumulative data considered within this paper.

#### 4.2.5.3. Psychotic Disorders

For the purpose of this Yellow Card data review, psychotic disorders encompass the following high-level group terms: Manic and bipolar mood disorders and disturbances, Psychiatric and behavioural symptoms not elsewhere classified (NEC), Psychiatric disorders NEC, Schizophrenia and other psychotic disorders. Psychotic disorders are the eighth most frequently reported psychiatric side effects suspected to be associated with isotretinoin treatment. There is a total of 107 UK cases of psychotic disorders up to a data lock point of 20 May 2021. Many of these patients reported additional adverse reactions including other psychiatric reactions.

*'My son and I had NO idea that Isotretinoin could trigger a psychotic reaction and it came as such a shock when it did.'*

*Comment received through call for information*

Research suggests that 9.8% of children and young people have experienced symptoms of psychosis (Sweeting, et al., 2015). Psychosis usually first emerges in young people between the ages of 15 and 30 years<sup>25</sup>. Men have a higher risk of developing schizophrenia during their lifetime<sup>26</sup>.

A study reported 38% of people recover after a first episode of psychosis, and symptoms improve for 58% of people (Arlington, 2013). Although 15 Yellow Card cases report resolution of psychosis, timeline for recovery is generally unavailable from the Yellow Card reports so it is difficult to

<sup>24</sup> Vizard T, Pearce N, Davis J, Sadler K, Ford T, Goodman R, et al. Mental Health of Children and Young People in England, 2017: Emotional disorders [Internet]. 2018 [cited 2019 Jan 7]. Available from: [digital.nhs.uk](https://digital.nhs.uk)

<sup>25</sup> [Mental Health of Children and Young People in England, 2017 \[PAS\] - NHS Digital](https://digital.nhs.uk)

<sup>26</sup> [Search - Beat \(beateatingdisorders.org.uk\)](https://www.beateatingdisorders.org.uk)

establish if the cases presenting with isotretinoin align with this. Improvements in early intervention and treatment methods, and newer medicines, mean better recovery rates for psychosis and schizophrenia. It is therefore paramount that events of psychosis are quickly identified and referred for specialist intervention. Approximately 20% of Yellow Card cases report side effects continuing after isotretinoin treatment completion/discontinuation, in some cases for many years. Although the SmPC outlines ‘discontinuation of isotretinoin may be insufficient to alleviate symptoms and therefore further psychiatric or psychological evaluation may be necessary’, many patients and parents have raised concerns that they were not provided with adequate or proportionate information on this potential risk. In the section on ‘Mental problems’ in the PIL, it further advises to ‘Contact your doctor straight away if you get signs of any of these mental problems. Your doctor may tell you to stop taking isotretinoin. That may not be enough to stop the effects: you may need more help, and your doctor can arrange this.’ This statement could be perceived by some as reassuring, that with additional help the effects will stop, which may not be the case for all patients.

The warning on psychotic disorders in section 4.4 of the SmPC states that psychotic symptoms have been reported in patients treated with isotretinoin. Psychotic disorder is also listed in section 4.8 of the SmPC as a very rare side effect ( $\geq 1/10,000$  to  $< 1/1,000$ ).

#### 4.2.5.4. Suicidal and self-injurious behaviours (excluding suicide)

##### 4.2.5.4.1. *Suicidal behaviour, suicidal ideation, suicide attempt*

A total of 192 UK cases reporting suicidal behaviour, suicidal ideation or suicide attempt were identified in the dataset at the data lock point of 20 May 2021. The mean age for Suicidal behaviour, Suicidal ideation and Suicide attempt are 21.75 years; 23.8 years and 20.22 years respectively.

*Over a period of about 3 months, I went from being a healthy, happy teenager to completely withdrawn from the world and suicidal. After attempting to end my life, I was admitted to a psychiatric hospital. I lost 3 years of my life, most of which I don't remember because I was so unwell, because of taking isotretinoin. I would much rather have had acne than have spent several years in hospital! The doctor who treated me and my family are certain that isotretinoin caused me to suffer from depression, withdrawal and suicidal thoughts.'*

*Comment received through call for information*

Among the general population, 20.6% of people have had suicidal thoughts at some time, 6.7% have attempted suicide, and 7.3% have engaged in self-harm. 26.8% of people aged 16 to 24 years report having had suicidal thoughts in their lifetime, a higher percentage than any other age group<sup>27</sup>. And 9% of 16 to 24 year-olds have attempted suicide in their lifetime – 5.4% of men and 12.7% of women.

34.6% of female individuals and 19.3% of male individuals aged 16 to 24 years report having thoughts of suicide in their lifetime. The gender distribution in the Yellow Card dataset differs from this with significantly more cases seen in male patients (114, 59%) than female patients (75, 39%), where gender was reported.

The limitations of spontaneous case reports are particularly apparent when considering the issue of suicidal behaviours. Many of the reports lack information regarding the patient's emotional wellbeing and whether risk factors for suicide are present. Not all cases of suicidal behaviours

<sup>27</sup> [Adult Psychiatric Morbidity in England - 2007, Results of a household survey - NHS Digital](#)

reported depression or symptoms of other psychiatric disorders and it is not known if changes in behaviour were masked by the patient, not recognised as a concern by the family and friends, or if the suicidal behaviour occurred impulsively.

Of those cases reporting time-to-onset of suicidal behaviours while on treatment, the majority (38 cases) report onset within the first 3 months of treatment. Some cases report persistence of suicidal behaviours for months and years after stopping isotretinoin.

The current warnings in the product information provide information on the risk of suicidal behaviours and advise patients to discuss their treatment with family and friends to help them identify changes in their behaviour and seek medical help straight away if they experience any mental health problems.

#### 4.2.5.4.2. *Self-injurious behaviours*

A total of 27 UK cases of self-injurious behaviours were identified in the dataset at the data lock point of 20 May 2021. The mean age for Intentional self-injury and self-injurious ideation is 22.43 and 22.5 years respectively.

The UK has one of the highest self-harm rates in Europe (Wood, et al., 2019). Self-harming behaviours can begin at any age, but commonly start between ages 13 and 15 years<sup>28</sup>. People who self-harm are approximately 49-times more likely to die by suicide (Solmi, et al., 2016), therefore, any emergence of self-harming behaviours while on isotretinoin treatment should prompt referral to psychiatric services.

#### 4.2.5.4.3. *Suicide*

There were 71 cases of death by suicide identified at the initial data lock point of 30 April 2020. Over the course of the review, a further 15 reports were received. Of these new cases, 10 did not provide a date of death and so it was difficult to establish if any were duplicates to those already in the database. It is important to note that some reports received through the Yellow Card scheme contain minimal information and the date of the suicide is not always provided. Despite attempting to obtain further information on cases, this is not always successful.

Cases of suicide are often reported by multiple parties including the patient's family, dermatologists, GPs or coroners and therefore multiple reports can exist for the same individual. Following careful review of the data and merging of duplicate cases there were a total of 83 UK cases of deaths by suicide at the data lock point 20 May 2021.

*'...he phoned and said he couldn't think properly or describe things he was normally fluent with. I told him I believed it was the Isotretinoin causing this and told him to stop taking it... This he did, but cruelly the adverse reaction continued to worsen even though he had stopped taking them. We had no idea how ill he was becoming, and... he had a severe psychotic reaction and hung himself in his lodgings... whilst his friends were in the next room.'*

*Comment received through call for information*

The mean age of people who died by suicide is 23.7 years (median 22 years), with the majority of cases in the age group 19 to 24 years (31 cases). One male of unknown age was also taking finasteride which has been linked to

<sup>28</sup> [Mental Health of Children and Young People in England, 2017 \[PAS\] - NHS Digital](#)

mood alterations and depression. Very few cases provided information on medical history, concurrent conditions and medications. Similarly, dose, duration of therapy and time to onset of events were not provided for most cases.

Suicide is the most common cause of death for those aged 10 to 19 years (Zipfel, et al., 2015). Other than a higher reporting rate observed in young male patients, no particular patterns or risk factors could be established from the Yellow Card data.

Concomitant adverse reactions associated with cases of completed suicide were depression, anxiety, personality change, suicide attempt, social avoidant behaviour, pain, suicidal ideation, psychotic disorder and skin reactions. No pattern of prodromal symptoms were identified. Considerable variability exists in relation to the reported temporal association between isotretinoin exposure and suicide. Time to onset ranged from 1 day following treatment initiation to 10 years post treatment.

Patients' families expressed concerns regarding suicides which have occurred in patients with no history of depression or other mental health issues and apparently no symptoms of depression or suicidal behaviour prior to suicide. Families expressed the view that if the risk of suicide cannot be avoided completely, then the risks outweigh the benefits of treatment and isotretinoin should stop being prescribed.

A number of reports highlighted minimal or no monitoring was undertaken in relation to psychiatric side effects throughout treatment. This is similar to the views expressed in the call for information.

Data from the Yellow Card scheme is published online with a Drug Analysis Profile (DAP) for each active substance. The DAPs are updated monthly to reflect the latest reporting data. During the review period there was considerable interest in the number of reports of suicide received through the Yellow Card scheme, as changes to both increase and decrease the number of reports were published as new cases were received or duplicate reports identified.

#### **4.2.6. Frequency of psychiatric side effects**

The Isotretinoin EWG questioned the listed frequency of psychiatric side effects in the isotretinoin SmPC given that these suggested the side effects occurred less frequently than the background rate in the general population. The MAHs were therefore asked to review the frequencies used to describe these side effects in the SmPC.

Peak age range for Yellow Card reports of psychiatric side effects is 15 to 25 years which reflects the age range where usage of isotretinoin would be highest. As described in literature, acne develops around onset of puberty and often increases in severity throughout puberty when sebaceous secretions increase. Peak age for acne, has been noted to be approximately 17 years. Acne generally tails off following puberty into young adulthood.

Acne is generally considered to appear at similar rates in male and female people, and literature and Yellow Card data demonstrate an increased incidence of psychiatric side effects on male individuals compared to those who are female.

Review of psychiatric events in other inflammatory dermatological conditions highlighted how chronic skin conditions have a significant impact on patients' health related quality of life, with high levels of psychological morbidity, as previously demonstrated with acne. Evidence from literature supports a high level of anxiety, depression and suicidal behaviours in patients with psoriasis. The range of prevalence of suicidal ideation in psoriasis was observed at between 2.4% and 9.7% and it commonly occurred in the context of depressed mood and anhedonia. Although the important

psychiatric comorbidities of anxiety and depression were high in this group, it was noted that this patient population was older in age and there was often a history of psychiatric illness observed in these patients. This is unlike the acne-patient population, who are younger and generally have fewer established psychiatric disorders.

None of the MAHs of isotretinoin products recommended any change to the frequencies of listed psychiatric disorders in the product information. Many noted that spontaneous data should not be used to assign side effect frequencies according to European guidelines, as this requires a data source where the size of the exposed population is known. They highlighted that the lack of controlled studies and occurrence of idiosyncratic events makes frequency estimation difficult.

Overall, adverse event reporting in initial clinical development programme for isotretinoin does not appear to have been systematic or robust. As the clinical trial programme was conducted primarily in the early 1980's, the design of these studies may not meet current standards. There was some improvement seen in the collection of adverse events and screening for psychiatric side effects in some of the more recent paediatric trials, with one of the clinical efficacy and safety studies reporting using the Beck Depression Inventory at baseline and at end of treatment. With regard to depression, very few individuals (adults and adolescents) demonstrated any change in score as a result of treatment with isotretinoin. No obvious differences were apparent between paediatric patients and adult patients in that study.

Based on the single case of depression reported in the initial clinical development programme of 423 patients receiving isotretinoin, frequency would be determined as uncommon ( $\geq 1/1,000$  to  $< 1/100$ ). However, this data was not sufficiently robust upon which to base frequency estimates for psychiatric disorders. Based on the later paediatric data, including 358 paediatric patients, frequency for depression would be classified as common ( $\geq 1/100$  to  $< 1/10$ ) and for each of suicide attempt, suicidal ideation and suicide, would be classified as uncommon ( $\geq 1/1,000$  to  $< 1/100$ ).

However, using this data to estimate frequencies for inclusion in the SmPC remains problematic due to a lack of systematic reporting and classification of adverse events. Furthermore, some of the clinical studies were too small ( $n=16/n=10/n=8$ ) to deduce any relevant safety information.

In the absence of good quality data on which to base updated adverse event frequency estimates in the SmPC, it is important that the extent of current knowledge, including the uncertainties, is made available to patients including contextual information on background rates of psychiatric morbidity.

### **4.3 Published literature**

The literature surrounding isotretinoin and possible psychiatric side effects is extensive. The literature review undertaken as part of the current Isotretinoin EWG review focused on the literature published since the last review of this issue by the CHM's Expert Working Group which concluded in 2014.

#### **4.3.1. Psychiatric disorders resulting from acne**

The effects of acne are both physical and psychosocial. Physical symptoms include soreness, itching, pain, scarring and post-inflammatory hyperpigmentation or depigmentation. Psychosocial effects include depression, suicidal ideation, anxiety, psychosomatic symptoms, shame, embarrassment, social inhibition, reduced attachment to friends, low self-esteem and overall impaired quality of life<sup>29</sup>, (Dellavalle R. , 2017), (Barnes , Levender, Fleischer Jr, & Feldman, 2012), (Dunn, O'Neill, &

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<sup>29</sup> [Overview | Acne vulgaris: management | Guidance | NICE](#)



Feldman, 2011). Psychological morbidity is compounded by multiple factors: acne effects are highly visible; popular culture and societal pressures dictate clear skin; acne can be dismissed by health-care professionals as a trivial self-limiting condition; and acne peaks in teenage years, a time crucial for building confidence and self-esteem (Williams, Dellavalle, & Garner, 2012).

One community-based study noted UK teenagers with definite acne (defined as moderate and severe acne consisting of 12+ lesions on the face) were almost twice as likely to score in the borderline or abnormal range on an age appropriate validated questionnaire of emotional wellbeing than did those who did not have acne (32% vs. 20%; odds ratio 1.86, 95% confidence interval 1.03 to 3.34) (Smithard, Glazebrook, & Williams, 2001). Acne can be associated with various psychiatric disorders such as anxiety, depression, and suicidal ideation in adolescents who are more psychologically vulnerable and susceptible to changes in their appearance (Cotterill & Cunliffe, 1997). Deteriorating physical appearance coupled with psychiatric comorbidity can have significant impact on quality of life. If psychiatric comorbidity goes undetected and untreated, the consequences may be serious (Erdogan, Erturan, Aktepe, & Akyildiz, 2019).

To assess the extent of psychological impact acne has on sufferers, an electronic acne questionnaire consisting of 14 multiple-choice questions, including questions on self-harm, suicidal ideation and emotional burden of acne was developed. The link to the survey was posted on the British Skin Foundation (BSF) website and the survey was also emailed to the BSF mailing list between January 2012 and November 2019. A total of 1610 people completed the survey; 70.7% of those completing the questionnaire with acne were female and the majority (73.2%) were aged between 15 and 35 years. Of those with acne, 60.5% experienced a fall in self-confidence and only 5.7% answered that acne had no impact on their day-to-day life. As a consequence of their skin disease, 31.0% of acne sufferers have been verbally abused on a few occasions by someone they know, 19.0% have been bullied on a regular basis and 18.7% have previously been verbally abused by another member of the public on numerous occasions. In total, 19.3% of acne sufferers have had a relationship end because of their acne. Concerningly, 20.1% have contemplated suicide and 4.0% have attempted suicide as a result of their acne. Further, 18.3% have self-harmed and 15.4% have thought about self-harming owing to their acne. The majority of acne sufferers in this study have tried acne products available from high street shops and only 16.3% have used isotretinoin. In total, 30.1% have tried 10 or more different types of treatment for their acne. Moreover, 78.1% answered that they would benefit from the BSF setting up a support line or support group for acne sufferers.

This study highlighted the serious impact acne has on mental health and it clearly showed that more can be done to address the accompanying psychological effects of acne in the UK (Ra, Ho, Bickerstaffe, & Bewley, 2020).

Recently, a US retrospective database study was conducted to explore the real-world relationship between patients with dermatologist-managed acne and subsequent diagnosis for depression, the non-acne dermatology population served as a control group. Outcome of interest was a diagnosis for depression (ICD-9/10 codes: 296.2, 296.3, 311; F32, F33) at least 1 month after acne diagnosis. Of 38,258 patients with acne, 1,830 (4.78%) had a diagnosis for depression compared to 5,894 patients with depression (4.96%) of the 118,849 in the control group (dermatologist managed patients with no-acne). Adjusted OR yielded a significantly decreased frequency of depression with acne (OR 0.84, 95% CI 0.79 to 0.89) compared to the control. Median time for onset of depression after acne diagnosis was 27 months (interquartile range 11 to 52), while onset of depression for non-acne controls was 43 months (interquartile range 16-83). The conclusion was that the acne population had a significantly lower prevalence of depression than the non-acne population, even after adjusting for age, sex, isotretinoin exposure (Soundararajan, et al., 2020). However, the control group of non-acne

dermatology patients may not be a representative group for the purpose of this review given the high prevalence of psychiatric disorders with other dermatological conditions.

#### **4.3.2. Depressive disorders with isotretinoin**

Evidence presented in the literature is somewhat conflicting regarding the nature of the association between the use of isotretinoin and the risk of depressive disorders. Historically, case reports, database studies, and retrospective studies show a possible association between isotretinoin and depression. Prospective studies, on the other hand, have shown no association or, in some studies, improvement of depressive symptoms. There are currently no randomised controlled trials specifically assessing the association between isotretinoin treatment and depression in patients with acne. There have been a number of meta-analysis, systematic reviews and review articles of varying quality as described below.

The most comprehensive systematic review and meta-analysis is that of Li, et al., (2019) which reviewed all studies (prospective, retrospective, nested case control, population based case-control study) published between 1984 and 2017, to investigate the association between the use of isotretinoin and the risk of depression in patients with acne. Altogether 20 studies were pooled into the meta-analysis. The number of participants using isotretinoin in these studies ranged from 16 to 7195. Except for two retrospective studies identifying patients with depression using the International Classification of Diseases code, all other studies were prospectively designed, and depression was assessed using depression symptom scales.

The heterogeneity of cohorts was explored by sensitivity, subgroup and meta-regression analyses. Most studies compared data before and after treatment, other than one which compared isotretinoin to vitamin C and a second which compared isotretinoin users to non-users. Most studies prescribed isotretinoin for moderate to severe acne and the dose ranged from 0.5mg/(kg/d) to 1.0mg/(kg/d). The duration of use of isotretinoin ranged from one to six months. Overall, the pooled data indicated no association between the use of isotretinoin with the risk of depressive disorders (Relative Risk [RR]=1.15, 95% CI 0.60 to 2.21, p=0.14). The association between the use of isotretinoin with the risk of depressive disorders was statistically significant on pooling retrospective studies (RR=1.39, 95% CI 1.05 to 1.84, p=0.02), but this association was not evident on pooling prospective studies (RR=0.85, 95% CI 0.60 to 2.21, p=0.86).

A number of sub-group analyses were undertaken, including by depression symptom scale used. The pooled results remained significant for studies using HADS-D and those using the Centre for Epidemiologic Studies Depression Scale (CES-D), however, the pooled effects were insignificant for studies using the BDI scale and those using the Hamilton rating Scale (HRS), demonstrating the variability between depression symptom rating scales. The study results revealed no new information on harm with use of isotretinoin and suggested an association for the use of isotretinoin in patients with acne significantly improved depression symptoms. Although overall considered to be a well conducted review, there were a number of limitations. Acne severity and dose of isotretinoin varied between studies and was not reported by several. The effects of acne severity, scarring and non-responders on depressed mood was therefore difficult to stratify. Analysis of confounders was deemed insufficient in most studies. A greater risk of depression was associated with use of isotretinoin on pooling the retrospective studies; however, selection and recall bias in the retrospective studies may have affected the incidence of depression.

Vallerand, et al., 2018 conducted a systematic review based on 11 trials to evaluate safety and efficacy of isotretinoin for acne. Eleven trials were identified (total 760 patients randomised),

containing mostly men. Mean treatment ages ranged from 18 to 47.9 years and participants generally had moderate-to-severe acne. Across all trials, isotretinoin therapy reduced acne lesion counts by a clinically relevant amount, and always by a greater amount than control, which was either placebo (two studies), oral antibiotics (seven studies) or other control (two studies).

Only six of the 11 trials planned a priori to monitor patients for any adverse events. Total adverse event frequency was approximately twice as high in the isotretinoin groups than in the controls. Overall, approximately two adverse events occurred per patient receiving isotretinoin and approximately one adverse event occurred per control patient. While the studies were too heterogeneous to perform meta-analysis, the three studies reporting the highest rates of adverse events (cheilitis most commonly) also used the highest doses of isotretinoin ( $1.0 \text{ mg kg}^{-1}$  per day) indicating a potential dose response relationship for adverse events. Psychiatric or psychosomatic adverse events were about 50% more frequent with isotretinoin use than in controls. Most commonly, this was documented as fatigue or lethargy. Overall, psychiatric or psychosomatic adverse events represented 32 of 751 (4.3%) adverse events for those treated with isotretinoin. Across all studies, there were two of 372 (0.5%) patients in the isotretinoin group who withdrew from the study due to psychiatric symptoms such as depressed mood, insomnia and hallucinations, although none of these cases were reviewed by a psychiatrist for diagnosis. A further participant was also noted to have withdrawn due to depressed mood during the open-label cross-over phase to isotretinoin.

Huang & Cheng (2017) meta-analysed 31 controlled or prospective studies published between 1984 and 2016 (providing prevalence of depression or depression score). In the controlled studies, the change in depression scores from baseline was not significantly different between patients receiving isotretinoin treatment and those receiving an alternative treatment (standardised mean difference [SMD] -0.334, 95% confidence interval [CI] -0.680 to 0.011). The prevalence of depression after isotretinoin treatment significantly declined (relative risk [RR] 0.588, 95% CI 0.382- 0.904). The mean depression scores significantly decreased from baseline (SMD - 0.335, 95% CI -0.498 to -0.172). No randomised controlled trials were reviewed and a large inter-study variation was observed. It was concluded that isotretinoin treatment for acne does not appear to be associated with an increased risk for depression. Moreover, the treatment of acne appears to ameliorate depressive symptoms.

Of the 31 studies reviewed in the Huang meta-analysis, 1 population-based study (Azoulay, et al., 2008) found that isotretinoin significantly increased the risk of depression (crude relative-risk 2.0; adjusted relative risk 2.68), and a further 2 open label studies (Ormerod et al, 2012 and Fakour, et al., 2014) found increased depression scores following isotretinoin (one significantly and one non-significantly). 10 controlled studies and 15 open-label studies found no association between isotretinoin use and the risk for depression. Eleven of the 25 studies showing no association found a significant improvement in the depression scores or a reduced frequency of depression following isotretinoin therapy. The remaining 3 studies only provided the prevalence of depression: 1) 11% mild depression after 1 month of therapy; 2) 4% prevalence of depression from the start to therapy completion; and 3) 0.9% during therapy which resolved with continued treatment. The authors highlight that the three population-based studies reviewed for inclusion underestimated the incidence of depression because diagnostic codes and antidepressant prescriptions were used as inclusion criteria and patients with inadequate data were excluded. Moreover, this underestimation might be particularly problematic for the study by Azoulay, et al., (2008) because the RR estimate was based on a small subset of patients who met strict depression and data availability criteria; therefore, the results might not be applicable to a general population of patients treated with isotretinoin. The study by Ormerod, et al., 2012, included patients  $\geq 16$  years with severe acne and no

pre-existing mental health problems. The study demonstrated nonsignificant trends toward an increased BDI score with isotretinoin treatment, however it was limited by a small sample size.

A review by Borovaya, et al., 2013 further highlights that studies on this topic have revealed conflicting results, and interpretations by different authors have varied. A total of 26 articles were reviewed (up to 2012), these articles vary in terms of study design, number of patients, therapy regimen, and even in their definitions of depression. An association between isotretinoin therapy and depression was investigated in 23 publications. In six papers, an association was reported to be likely; however, 17 studies found no association. The authors describe how the similarity between the biochemical structures of vitamin A and isotretinoin explains the analogous side effects. The classical symptoms of hypervitaminosis A being anger, aggression, sadness, mood swings, loss of concentration, irritability, depression, and psychosis.

Five individual studies published in the period since the previous Expert Working Group review in 2014 reported an association between isotretinoin treatment and depression, including two prospective studies (Al Alawi, et al., 2018), (Botsali, Kocyigit, & Uran, 2020), (Lafay-Chebassier, et al., 2015) (Fakour, et al., 2014) (Nikam, Jamale, & Ravikumar, 2020) However, 13 studies not only showed no increased risk of depression in patients with acne in comparison to the general population and/or control groups, many also showed isotretinoin treatment improving mood and levels of depression (Metekoglu, Oral, Ucar, & Akalin, 2019) , (Marron & Tomas-Aragones, 2013) (Metekoglu, Oral, Ucar, & Akalin, 2019) (Bray, Kravvas, Skevington, & Lovell, 2019) (Simic , Penavic, Babic, & Gunaric, 2017); (Erdogan, Erturan, Aktepe, & Akyildiz, 2019) (Suarez , Serrano, Cova, & Baptista , 2016), (Huang & Cheng, 2017) (Al Ghofaili, 2021), (Algamdi, et al., 2020), (Botsali, Kocyigit, & Uran, 2020), (Ozkur, Kivanc Altunay, Celik, Sekerlisoy, & Falay, 2020), (Hekmatjah, et al., 2020).

Several case reports or case series discussed individual experiences of depressive disorders following use of isotretinoin and highlighted the complexity of management in treating different risk groups, including those with a history of depression, family history of depression, co-morbid conditions and treatment in transgender groups.

These studies do not provide any significant new information regarding the risk of depressive disorders which is not already included in the product information.

The literature highlights that a minority of patients may be susceptible to severe mood deterioration on isotretinoin. Studies have attempted to further investigate this vulnerability; however, a worsening of mood could not be associated with any of the measured baseline traits (Bray, Kravvas, Skevington, & Lovell, 2019). Acne itself is associated with depressive symptoms making studies on the topic difficult to design and interpret. Highlighted risk factors for clinically relevant mood deterioration are personal or family history of psychiatric disorders (or both), severity of acne at initiation, presence and severity of other side effects from isotretinoin.

#### 4.3.2.1 Studies demonstrating an association

##### 4.3.2.1.1 *Prospective studies*

Botsali, et al., 2019 conducted a prospective, non-randomised study to evaluate the impact of isotretinoin on neurocognitive functions in adolescents with acne and to determine the emergence of psychiatric events (depression and anxiety). The study, conducted in a Turkish population age 12-18 years, included 55 patients with moderate and severe acne (grade 3 and 4) prescribed isotretinoin versus systemic antibiotic treatment. Groups were not matched for acne severity, with the

isotretinoin group having more patients with severe acne. The isotretinoin group exhibited a small statistically significant increase in depression throughout the study follow-up, mostly observed in the first 3 months, based on the self-reported questionnaires. However, no patients were evaluated as depressed by the formal psychiatric evaluation. At 6 months of treatment, results showed an improvement in neurocognitive function in the isotretinoin group compared to baseline and State and Trait Anxiety Scores were stable ( $p=0.749$ ,  $p=0.124$ ). In the antibiotic group State Anxiety Inventory scores decreased from baseline ( $p=0.013$ ), demonstrating reduced anxiety and Trait Anxiety Inventory and Cognitive Distortions Scale (CDS) scores remained stable.

A prospective, non-controlled study by Fakour, et al., (2014) enrolled 98 patients suffering from severe acne (38 males and 60 females). Treatment of acne with isotretinoin was associated with significant improvement of self-assessed quality of life scores in both male and female patients ( $p = 0.001$ ). Considering the cut-off value of 13 for mild depressive mood in the Beck Depression Inventory (BDI) score, in total, 48 (49%) of the enrolled patients (21 males and 33 females) had a mild depressive mood before the commencement of the treatment in this study, which the authors attribute to having acne. The analysis of before and after treatment BDI scores showed that the number of patients identified as depressed and also the mean score of BDI (severity of depression) were increased in both male and female patients after the treatment ( $p<0.05$ ) in spite of the improvement in quality of life scores. The inclusion of patients with only severe acne may explain the relatively higher depressed mood at commencement of study; in the absence of a control group, this may have an impact on the generalisability of the results (Al Ghofaili, 2021), (Algamdi, et al., 2020).

An Indian prospective observational study exploring the association of isotretinoin with anxiety and depression in the Indian population used Hamilton anxiety rating scale (HAM-A) and Montgomery Asberg Depression Rating scale (MADRS) at baseline up until the fourth visit (12 weeks). Out of the 300 patients, majority of the patients (70.8%) were in the 21 to 30 years age group. Significant increase in MADRS score was observed at baseline to final visit ( $p < 0.05$ ) with mild and moderate depression in 4 (1.3%) and 2 patients (0.6%), respectively. On the contrary, a significant decrease in HAM-A score was observed over the visits ( $p < 0.05$ ). This demonstrated an improvement in anxiety (attributed to improvement in disease severity), a negligible association was found with depression, none of the patients reported any suicidal tendencies (Nikam, Jamale, & Ravikumar, 2020).

#### 4.3.2.1.2 *Retrospective studies*

Al Alawi, et al., 2018 estimated the prevalence of depression among a random sample of dermatological patients in an Omani hospital. Regression analysis showed isotretinoin, in addition to family history of depression and comorbid medical disorders, to be a significant predictor of depression (OR = 2.78; 95% CI: 1.08-7.19,  $p = 0.035$ ), among patients with dermatological disorders. However, the authors reported that they considered the self-rating scale used, the Patient Health Questionnaire-9 (PHQ-9), to be a limitation and that future studies should employ a gold-standard interview to solicit the presence of depressive symptoms. This study was also unable to rule out possible pre-existing depressive symptoms.

Lafay-Chebassier, et al., 2015 used the case/no case method in the French pharmacovigilance database (FPVD) to identify drugs reported in association with depression over a 5-year period. Data were expressed as reporting odds ratio (ROR) with their 95% confidence interval. Out of a total of 474 reported cases of depression, 57 reports were identified in association with isotretinoin. Taking into account the 298 validated ADR reports for isotretinoin in the FPVA this gives a reporting odds

ratio of 64.7 (47.7-87.6)  $p < 0.001$ . In 6 cases overall, depression led to the death of the patients by suicide; in 4 of these the patients were treated with isotretinoin.

### **4.3.3. Suicidality**

Well-designed, blinded, randomised controlled trials are required to provide scientifically sound, evidence-based data on this safety concern. However, this is logistically difficult due to potential ethical concerns associated with using suicide as a study end point (McGrath, et al., 2010) and practical (blinding) considerations relating to randomisation given the superior efficacy of oral isotretinoin in the treatment of acne and its range of side effects (Oliveria, 2018), (Bremner, et al., 2012), (Rea, et al., 2018).

A number of large studies have been published since the 2014 review to further investigate this safety concern; these include reviews of studies published before 2013 and so there is some overlap in data with previous reviews.

Oliveria, et al., 2018 reviewed the current literature regarding the association between isotretinoin and depression and suicide published between 2005 and 2016. The authors noted that although case reports and database studies show a clear association, which is biologically plausible, prospective studies have opposing results showing no association or, in some studies, improvement of depressive symptoms. Some of the literature reviewed showed that depression and suicide appears commonly 1 to 2 months after treatment initiation. Oliveria, et al., suggests that the biological mechanism may not be via immediate influence of isotretinoin on a crucial neurotransmitter or other signal pathway but may be through a secondary system or possibly alteration of neuroplasticity or a metabolic process known to be influenced by retinoic acid. Alternatively, they speculate that changes in neurochemical systems may occur more rapidly, but it may take weeks or months before a behavioural effect is seen, as is the case with antidepressants. The authors acknowledge that despite the negative results of prospective studies, cases reporting positive rechallenge provide a very strong indication that there is at least a subset group of patients with vulnerability to isotretinoin. They go on to state that such patients are probably excluded from most prospective studies, which often exclude patients with a personal or family history of mental disorder. In addition, it is possible that successful treatment with isotretinoin may improve depressive symptoms in severe cases of acne (possibly by improving self-image), obscuring the fact that the drug is negatively affecting a small number of patients. In fact, while some of the prospective studies reviewed describe cases of depression with isotretinoin, globally there was no association. The authors considered that sample sizes were not large enough to assess this question and that in many cases, depression may be an unrelated event, caused by acne or a number of other factors. On the other hand an effect on certain individuals is supported by cases reporting rechallenge (and which may point to, at least, an idiosyncratic reaction) as well as by reports that higher doses of isotretinoin are associated with a greater risk of depression. The authors suggest that the different views of dermatologists and psychiatrists described in the literature could also have resulted in recruitment bias in some studies. They conclude that no firm conclusion can be drawn from the literature but it appears there are a group of individuals who are at risk of developing depression and/or suicide, particularly those with a personal or family history. While it therefore seems appropriate for all patients on isotretinoin to be regularly screened for depressive symptoms and suicidal ideation and promptly referred to mental health professionals if symptoms arise, further studies are required to confirm which patients would benefit from early referral to a mental health professionals on isotretinoin initiation.

The systematic review by Gorton, et al., 2016, on non-psychotropic medication and risk of suicide or attempted suicide included two studies relating to isotretinoin, both of which were considered by the previous EWG (Jick, et al., 2000 & Sundström, et al., 2010). This study further aimed to quantify the influence these medications have on this risk, beyond that conferred by underlying illness. The authors noted that no difference in the combined risk of attempted and completed suicide was associated with isotretinoin or antibiotics, compared to non-exposure, regardless of psychiatric history. This study reported relative risk estimates of approximately 1.0 for the comparison of isotretinoin use or oral antibiotic use with non-exposure to either drug for newly diagnosed depression or psychosis, regardless of the data source. Similarly, relative risk estimates were all around 1.0 for isotretinoin when comparing before treatment with after treatment. The relative risk estimate for suicide and attempted suicide was 0.9 (95% confidence interval, 0.3-2.4) when comparing current isotretinoin exposure with non-exposure. This study included more than 7,000 isotretinoin treated patients; 340 of which were from the UK. (Jick, et al., 2000, Gorton, et al., 2016).

Similarly, they noted there was no significant difference in attempted suicide risk before treatment compared to 6 months after treatment, in Sundström et al's cross-over analysis. In the study period 128 patients were admitted to hospital for attempted suicide. During the year before treatment, the standardised incidence ratio for attempted suicide was raised: 1.57 (95% confidence interval 0.86 to 2.63) for all (including repeat) attempts and 1.36 (0.65 to 2.50) counting only first attempts. The standardised incidence ratio during and up to six months after treatment was 1.78 (1.04 to 2.85) for all attempts and 1.93 (1.08 to 3.18) for first attempts. Three years after treatment stopped, the observed number of attempts was close to the expected number and remained so during the 15 years of follow-up: standardised incidence ratio 1.04 (0.74 to 1.43) for all attempts and 0.97 (0.64 to 1.40) for first attempts. 32 patients made their first suicide attempt before treatment of whom 12 (38%) made a new attempt or committed suicide thereafter. By contrast, 14 patients made their first suicide attempt within six months after treatment stopped of whom 10 (71%) made a new attempt or committed suicide during follow-up. The point estimates of the standardised incidence ratios rose gradually from three years before treatment through to the year immediately before treatment. However, none of these point estimates was statistically significant. The risk was significantly raised only six months after the end of treatment. Two to three years after treatment, the observed number of suicide attempts was close to the expected number.

Considering the increasing risk of attempted suicide during the years before treatment, the authors could not determine whether the continued rise during and immediately after treatment was due to the natural course of severe acne or to negative effects of the treatment. The authors conclude that at the level of the population, the results indicate that treatment with isotretinoin may attenuate suicidal behaviour. However, for certain vulnerable patients, isotretinoin may trigger such behaviour and the most important proactive measure to take would be to closely monitor all patients' psychiatric status during treatment and for at least a year after treatment with isotretinoin.

Gorton, et al. concluded that overall, the contribution of corticosteroids, isotretinoin and antiepileptic drugs to the risk of suicide and attempted suicide remains unresolved.

Three large database studies, published since 2013, conducted in France (Droitcourt, et al., 2019) and the USA (Singer, Tkachenko, Sharma, & Barbieri, 2019) and (Ugonabo, et al., 2021) suggested that the rate of suicide among patients taking isotretinoin may be lower than that of the general population. Droitcourt and colleagues also found no evidence for a triggering effect of isotretinoin initiation on suicide attempt. It is possible that selection of patients at lower risk for suicidal behaviour and appropriate treatment management could at least partly explain these findings, as patients with a history of depression and previous suicide attempts were excluded from the study.

The Droitcourt (2019) study, a comprehensive case series of suicides and suicide attempts under isotretinoin, and a case–control study (n=328,018), using Nationwide French Health Insurance database found suicide attempts under isotretinoin were rare events, and results suggested that most of the patients concerned have a risk-prone profile detectable at the time of treatment initiation. In the multivariate analysis, psychiatric history and history of anxiety alone were risk factors for suicide attempts (ORs 18.21, 95% CI, 9.96 to 33.30; and 4.78, 2.44–9.33, respectively). This highlights the importance of initial psychiatric screening prior to treatment initiation via standardised tools and further monitoring throughout treatment to easily establish emergence of symptoms, allowing for treatment modification where required.

Evaluation of all psychiatric side effects (including suicide) reported in patients taking isotretinoin between 1997 and 2017 in the FDA Adverse Event Reporting System used data from the iPLEDGE program (a risk management system which records all patients prescribed isotretinoin in the USA) to calculate the rates of completed suicide per 100,000 patients registered in iPLEDGE in those years (Singer, et al., 2019). A total of 17,829 psychiatric adverse events with isotretinoin as the primary suspect drug were reported to the FDA from 1997 through 2017; 50.1% of these adverse events occurred in males, 46.9% occurred in females, and 3.0% did not report the patient's gender. Depressive disorders (n=7547; 42.3% of all psychiatric adverse event reports), emotional lability (n=2962; 16.6%), and anxiety disorders (n=2412; 13.5%) were the most commonly reported adverse events. In addition, there were 2278 reports of suicidal ideation (12.8% of all psychiatric adverse event reports), 602 reports of attempted suicide (3.4%), and 368 reports of completed suicide (2.1%). Males accounted for 52.5% and 51.0% of reports of suicidal ideation and suicide attempts, respectively, and 78.8% of completed suicides. The authors acknowledge that this gender-specific disparity is consistent with national statistics on completed suicide in the United States. Among these reports, the highest number of any reported adverse event occurred in patients aged 10 to 19 years old. This age group accounted for 52.5% of the total psychiatric adverse events, and had 164 completed suicides, accounting for 57.7% of completed suicides where the age was reported. The authors outline that this could reflect more isotretinoin prescriptions in this age group or may suggest that teenagers are particularly vulnerable to psychiatric adverse events while taking isotretinoin. In 2009 and 2010, there were 21 and 11 completed suicides, respectively indicating a rate of 8.4 suicides per 100,000 patients enrolled in 2009 and 5.6 suicides per 100,000 patients enrolled in 2010. These rates are lower than reported national suicide rates in the United States for these years, which were 11.8 per 100,000 people in 2009 and 12.1 per 100,000 people in 2010 for the general population and 10.2 per 100,000 people in 2009 and 10.5 per 100,000 people in 2010 for those aged 15 to 24 years. The authors concluded that depressive disorders and suicidality were the most frequently reported adverse events associated with isotretinoin use, but these reports must be considered in the context of elevated rates of depression and suicide among patients with acne. The study suggests that the rate of completed suicide in patients taking isotretinoin may be lower than that of the general US population, but further study is necessary to assess the rate of completed suicide in this population. The authors propose that the mandated monthly visits under the current iPLEDGE infrastructure may provide an opportunity to screen patients for psychiatric conditions and improve patient outcomes.

A retrospective cohort study was conducted using the IBM Market Scan Research Databases, which contain commercial insurance claims in the United States, to identify patients with acne who were prescribed isotretinoin or oral antibiotics between 2011 and 2017 and who were diagnosed with psychiatric disorders or suicidal behaviour. A total of 72,555 patients aged 12 years or older were included in the study. This study found no evidence of increased suicidal ideation or of suicide attempts in patients treated with isotretinoin compared to those treated with antibiotics only or



those in the general population (Ugonabo, et al., 2021). Patients in the general population were 1.47-times more likely to be diagnosed with suicidal ideation or attempt compared to patients with acne prescribed isotretinoin. When adjusted for age, sex, and number of days enrolled, the general population (adjusted OR 0.87, 95% CI 0.84 to 0.89;  $p < 0.0001$ ) and patients with acne prescribed antibiotics (adjusted OR 0.88, 95% CI 0.85 to 0.91;  $p < 0.0001$ ) were less likely to have a psychiatric diagnosis compared to patients with acne prescribed isotretinoin. The prevalence of suicidal behaviour during isotretinoin treatment was lower (0.10%;  $p = 0.082$ ) than in the year prior to isotretinoin treatment (0.22%) and in the year following treatment (0.34%;  $p = 0.004$ ). Although the data demonstrate a lower prevalence of suicidal behaviour in patients prescribed isotretinoin compared to the general population, the study did find an increase in suicidal behaviour after cessation of treatment among patients prescribed isotretinoin. Because data collection started 30 days after the last isotretinoin prescription was filled, this number is unlikely to represent discontinuation due to suicidal behaviour. This difference was statistically significant, and a similar trend was not observed in the antibiotics only cohort. Further exploration into the slight increase in suicidal behaviour seen in isotretinoin patients 1 year after therapy is warranted (Ugonabo, et al., 2021).

While these large studies provide some reassurance, the negative association in these studies must be interpreted with caution and consideration given to how the data was captured, exclusion criteria, bias and the resulting potential for underestimation of the risk.

The other prospective studies identified examining the potential association between isotretinoin and suicide since 2013 have generally been lacking in power or lacked control groups.

A randomised controlled trial for safety and efficacy of low-dose isotretinoin for the treatment of anogenital warts ( $n = 46$ ) observed no suicidal ideation detected with the Columbia-Suicide Severity Rating Scale (C-SSRS), however numbers were low in the isotretinoin group at 23 participants (Reyna-Rodriguez, et al., 2021).

Nevoralova and Dvorčáková 2013, conducted a single centre, no-blind, and non-controlled prospective study between 2006 and 2008 among outpatients aged over 12 years and suffering from moderate to severe acne presenting at an acne clinic (Nevoralova and Dvorčáková 2013). Participants completed the Beck Depression Inventory, Version II (BDI-II) at baseline and at months 1, 4, 7, and 9 (the final month of isotretinoin therapy for some patients). Total scores were assessed, and particular attention was paid to items 2 (pessimism) and 9 (suicide ideation) in view of risk for suicide. All questionnaires were checked by a psychiatrist. 100 patients were included in the study, of whom 71 (71%) were male and 29 (29%) were female. The mean age of the patients was 18.1 years (range: 12–41 years). A significant improvement in BDI-II scores was observed between months 0 and 1, 4 and 7, and 0 and 9 (9 being the final month of therapy for some patients), respectively, in the whole tested group ( $p < 0.001$ ), and also in male and female patients separately ( $p < 0.05$  for both). Between months 1 and 4, BDI-II scores were observed to deteriorate in the whole group and in female subjects but to improve in males. Neither the worsening nor the improvement was statistically significant. Between months 7 and 9, an improvement in BDI-II scores was observed in all the monitored groups but was statistically significant only for male subjects. Mean BDI-II scores for female patients were higher than those for male patients at baseline and also at months 1, 4, 7, and 9, but the difference was not statistically significant. The authors concluded that their prospective study found no patient with significant depressive symptoms caused by isotretinoin treatment. No risk for suicide was found during follow-up, and there was no occurrence of suicidal ideation. This study is, however, limited by its methodological approach and size.

#### 4.3.4. Psychotic disorders

A link to psychosis and exacerbation of bipolar disorder with isotretinoin is less extensively addressed in the literature. Isotretinoin as a trigger in patients with previous neuropsychiatric history has been explored in previous literature; however, conclusions are variable. Publications highlight that misdiagnosis can occur in the case of psychotic disorders, whereby, patients self-reporting as depressed may be displaying symptoms of mixed mood episodes or mania (Fornaro, 2010).

A comprehensive review article by Truitt (2018) sought to explore whether some patients previously reported as experiencing isotretinoin-induced depression may have instead been experiencing symptoms of mixed mood, mania or psychosis. Upon a thorough review of the literature (1982-2018), the authors found that many of the papers describing patients with depression also had signs of psychosis, mania, mixed mood symptoms, activation, irritability, and/or agitation. One of the difficulties identified in reviewing patients' psychiatric symptoms is the use of vague terminology such as: personality changes, mood swings, and psychological changes. These ambiguous terms can describe either mood elevation or depression. Unfortunately, many of the reports reviewed in this study provided no formal diagnosis from a mental health professional, and due to the vague use of terminology, the authors concluded it was difficult to know if patients were indeed suffering from depression, as reported in many studies, or other symptoms such as mania or psychosis.

The authors highlight that health professionals not experienced in mental health may lack the training to take detailed psychiatric histories or to differentiate between complex presentations, such as mixed mood states potentially leading to misdiagnosis. This was also noted by Daunton, et al., (2019) discussed in section 4.3.7 below.

Another notable observation made by Truitt was that many studies that reported patients having isotretinoin-induced psychosis/mania had a history of mental illness, which may suggest a possible genetic susceptibility to these psychiatric effects. However, as there are case reports of psychosis in the absence of family history the authors outline it is still possible that isotretinoin can cause psychosis and mania in those who are not genetically predisposed, but the risk greatly increases in those who are predisposed. The authors advise that further studies are warranted, particularly, the relationship between isotretinoin and mania needs to be explored further using prospective, randomised controlled trials. The authors advocate for dermatologists to consider taking a more detailed mental health history of the individual and biologically related family members prior to starting treatments; for clinicians to consider monitoring for symptoms of mania and psychosis throughout and after discontinuation of the medication; and in the case of high-risk patients for the dermatologist to collaborate with a mental health professional (Truitt, et al., 2018), (Daunton, et al., (2019)

A small study on the relationship between isotretinoin and affective disorders (Hanna, et al., 2016) in 9 patients who were diagnosed with AD temporally associated with the use of isotretinoin preparations reported the mean time from the first use of isotretinoin to the onset of mental disorders was approximately 2 months (1 – 6 months). The mean time from the initiation of isotretinoin treatment to a visit with a psychiatrist was about 12 months (from 1 to 38 months). The time from the beginning of isotretinoin treatment to its discontinuation was on average 4.5 months (ranging from 1 to 12 months). The authors suggest that this may simply reflect the duration of the treatment course rather than stopping isotretinoin treatment due to suspected adverse reactions. The predictors of occurrence of affective disorders included a family history of affective disorders and a prior episode of mental disorders. The onset of affective disorders was in most cases preceded by prodromal symptoms such as headaches, sleep disorders, fatigue, drowsiness, or general weakness. Five patients reported suicidal ideation, four patients showed suicidal tendencies, and two patients attempted to commit suicide during the treatment. The authors concluded in light of the review of current literature and the cases analysed in this paper, that in these 9 cases an

association between isotretinoin treatment and the occurrence of affective disorders could not be ruled out.

A recognised prodrome to psychosis has been further described in the literature (based on the North American Prodrome Longitudinal Study) with some predictive validity, including emergence of avoidant, schizotypic, paranoid, narcissistic, obsessive-compulsive and other personality disorders (Larson, Walker, & Compton, 2010), (Addington, Coldham, Jones, Ko, & Addington, 2003), (Addington & Heinssen, 2011) but data showing any association between a psychotic prodrome and isotretinoin are currently lacking.

A number of case reports in the literature also describe individual occurrences of isotretinoin-induced psychosis, demonstrating a dose-response relationship, positive de-challenge and absence of any personal or family history of neuropsychiatric conditions (Lucca et al (2016), Rajagopal (2014), (Jensen & Abba-Aji, 2020), (Elhusein, et al., 2020).

#### **4.3.5. Influence of dose on psychiatric side effects with isotretinoin**

Isotretinoin is often initiated at a dose of approximately 0.5 mg/kg per day when treating severe acne. The dose is then increased toward 1 mg/kg per day, if tolerated by the patient, as adverse effects often increase with higher doses. The standard dosing regimen (achieving a cumulative dose of 120–150 mg/kg over a 4 to 6 month time period) is associated with some recurrences of acne but there are limitations of previous studies. The current recommendation based on a consensus statement from the Global Alliance to Improve Outcomes in Acne (Thioboutot, et al., 2018) is to treat until the acne is clear and continue for 1 more month. Patients with more severe disease may require higher cumulative doses (Landis, 2020).

High, low, and low intermittent dosing regimens have been reported to be well tolerated and with varying degrees of efficacy. Blasiak, et al., (2013) described how high cumulative doses of isotretinoin (greater than 220 mg/kg compared with lower than 220 mg/kg) may decrease relapse rates and the need for repeat courses of treatment. In their prospective observational study, they found an unadjusted relapse rate of 26.9% for patients who received 220 mg/kg or higher of isotretinoin, and an overall relapse rate of 1.7%. The adjusted relapse rate (43.8% versus 26.6%;  $p=0.22$ ) was not statistically significant, likely because of the small sample size. Cumulative dosing appeared to be well tolerated, only rash was more common in the higher-treatment-dose group. No patients in the study without previous psychiatric history reported suicidal ideation, and there was no significant difference between the dosing groups. However, it is unclear if psychiatric monitoring by a validated tool was undertaken routinely throughout the study. One patient was reported as discontinuing due to worsening low mood.

Low-dose intermittent and fixed low-dose regimens of isotretinoin have been used with varying degrees of success for acne, mostly mild to moderate acne. The low-dose intermittent regimen has been proven to be well tolerated (Agarwal, Besarwal, & Bholra, 2011) and effective for treating acne and consists of 0.5 mg/kg per day for 1 week every 4 weeks for a treatment course of 6 months (Kaymak & Ilter, 2006), (Akman, et al., 2007) Fixed low-dose regimens have varying protocols; 20 mg daily and 20 mg every other day can be effective in moderate acne (Sardana & Garg, 2010). Low-dose and intermittent dose regimens report decreased frequency and severity of mucocutaneous adverse effects, decrease of overall adverse effects, including psychiatric effects, and increased patient compliance. However, long-term relapse rates are unknown.

*'My dose was doubled from 30mg to 60mg at the beginning of my second month. Within a few days I became seriously psychologically ill and in no way were these problems related to the condition of my skin.'*

*Comment received through call for information*

A dose-dependent response for isotretinoin and psychiatric side effects has not been formally established. Studies of alternative regimes have generally focused on relapse rates and overall side effects. Few have included systematic structured psychiatric monitoring as part of their protocols. It is, therefore, difficult to establish the benefit of alternative treatment regimens on emergence of psychiatric side effects from literature.

A prospective study of 40 patients on short-course low-dose oral isotretinoin (0.5 mg/kg per day for 2 months) and 40 age and gender matched controls (aged between 12 and 50 years) treated with a systemic antibiotic (doxycycline 100 to 200 mg per day) and a topical retinoid (adapalene 0.1%) were enrolled in this study to examine frequency of depression in patients with acne vulgaris treated in Iran. The depression score was measured based on Beck's Depression Inventory (BDI) in both groups before and after 2 months of treatment and BDI score and the rate of depression were not significantly different between the two groups after the 2 month treatment period. Moreover, the authors did not find any significant change in BDI score in each group after treatment ( $p > 0.05$ ) (Nikneshad, et al., 2020).

The recently published NICE guideline on acne vulgaris management (June 2021)<sup>30</sup>, has made the following recommendations regarding dose of isotretinoin.

Isotretinoin should be prescribed at a standard daily dose of 0.5 to 1 mg/kg. NICE advise considering a reduced daily dose of isotretinoin (lower than 0.5mg/kg), for people at increased risk of experiencing adverse effects. They state that the risk of adverse events is multifactorial, and so assessment of risk would be dependent on the person's circumstances and could not be quantified as part of the recommendation.

NICE suggest when giving isotretinoin as a course of treatment for acne:

- Continue until a total cumulative dose of 120 to 150mg/kg is reached, (the evidence showed that total cumulative doses of at least 120mg/kg in a single course were more effective compared with total cumulative doses lower than 120mg/kg in a single course)

but

- If there has been an adequate response and no new acne lesions for 4 to 8 weeks, consider discontinuing treatment sooner.

The committee for the NICE acne guideline noted that evidence for lower dose oral isotretinoin was scarce, and therefore this was prioritised as one of the key recommendations for research. The suggested research question was: What is the efficacy of reduced dose oral isotretinoin in the management of acne vulgaris?

#### **4.3.6. Guidelines and consensus statements**

The consensus document by Dessinioti, et al., (2020) included a review of the association between isotretinoin and depression in the selected international guidelines and a further consideration of the available literature. This focused on four main guidelines: European S3, French, American Academy of Dermatology (AAD), and Canadian, with publication dates ranging from 2015 to 2017.

<sup>30</sup> [Overview | Acne vulgaris: management | Guidance | NICE](#)

The European Guidelines<sup>31</sup> state that there is continued uncertainty regarding isotretinoin, depression and suicidal behaviour and that caution and patient information appears reasonable. It is mentioned that the current literature comes to different conclusions and that there were important limitations in studies. They recommend assessing prior symptoms of depression in the patient's medical history before isotretinoin onset and during treatment and to inform patients about a possible risk of depression and suicidal behaviour. The Canadian guidelines (Asai, et al., 2016) were adapted from the European guidelines (version 2012). There were no specific recommendations provided relating to mood changes or depression.

The French guidelines<sup>32</sup> mention that no available population level data support that isotretinoin increases the risk of depression in, or suicide attempts by, patients suffering from acne. However, it is stated that a rare individual risk could not be excluded and that before initiation of isotretinoin treatment, the patient and his/her family must be informed of the potential risk of psychiatric disorders and the treating physician must be notified of any mood or behaviour change.

The AAD guidelines (2016)<sup>33</sup> mention that, although mood changes, including depression, and suicidal behaviour have been reported sporadically, there are no studies to suggest an evidence-based link between isotretinoin and depression, anxiety, mood changes, or suicidal ideation/suicide. However, it is proposed that prescribing physician should continue to monitor for these symptoms and make therapeutic decisions within the context of each individual patient.

Dessinioti, et al., addressed a number of important clinical questions regarding isotretinoin treatment, including type of acne indicated, age indicated, recommended daily dose, cumulative dose, consideration for timing of other procedures, essential duration of contraception after discontinuation, association with depression, association with inflammatory bowel disease, recommendations for preventing acne flares during treatment, and recommendation for laboratory monitoring (Dessinioti, Zouboulis, Bettoli, & Rigopoulos, 2020).

The Brazilian Society of Dermatology conducted a consensus review on the use of oral isotretinoin in dermatology. There was agreement about the efficacy of oral isotretinoin in the treatment of acne, including as an adjunct in the correction of scars. Common and manageable adverse events were considered mucocutaneous in nature. Others, such as growth retardation, abnormal healing, depression and inflammatory bowel disease have been thoroughly investigated, and there was no evidence of a causal association; they are rare, individual, and should not contraindicate the use of the drug. Regarding unapproved indications, it may represent an option in cases of refractory rosacea, severe seborrheic dermatitis, stabilisation of field cancerization with advanced photoaging and, although incipient, frontal fibrosing alopecia. For keratinisation disorders, acitretin performs better. In the opinion of the authors, indications for purely aesthetic purposes or oil control are not recommended, particularly for women of childbearing age (Bagatin, et al., 2020).

#### **4.3.7. Isotretinoin Prescribing UK**

A recent survey of members of the Scottish Dermatology Society to assess dermatologists' perception and experience of mood disturbance in patients taking isotretinoin for acne showed that 65% of respondents (n=48) prescribe isotretinoin at least weekly. 63% of practitioners believe

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<sup>31</sup>European evidence-based (S3) guideline for the treatment of acne- update 2016- short version  
<https://onlinelibrary.wiley.com/doi/epdf/10.1111/jdv.13776>

<sup>32</sup> Guidelines for the management of acne: recommendations from a French multidisciplinary group  
<https://onlinelibrary.wiley.com/doi/epdf/10.1111/bjd.15843>

<sup>33</sup> ADD Guidelines of care for the management of acne vulgaris  
[https://www.jaad.org/article/S0190-9622\(15\)02614-6/fulltext](https://www.jaad.org/article/S0190-9622(15)02614-6/fulltext)

isotretinoin can cause depression. Some 71% estimate that depression after isotretinoin prescription is infrequent (<1% of their practice), but the same proportion (71%) are concerned about the mental health of their patients taking the drug. The majority (87%) have previously stopped isotretinoin prescription due to mental health concerns, but their concerns are predominantly centred around isotretinoin-induced anxiety (71%) rather than suicidal ideation (2%). The majority of dermatologists (94%) do not feel fully confident in assessing the psychiatric status of a patient taking isotretinoin, and 75% do not use any tools to aid mental wellbeing assessment in these patients. Most (92%) involve psychiatry infrequently (<10% of cases) and 71% ask about suicidal thoughts in patients on isotretinoin only if low mood is present. Reassuringly, the vast majority of practitioners did not report a suicide of a patient taking isotretinoin (2 cases over a cumulative total of over 600 years of clinical practice). The authors propose using the Hospital Anxiety and Depression Scale and Patient Health Questionnaire-9 tools to assist mental status evaluation. Discussion to define indications for referral to psychiatry and when to stop isotretinoin is needed (Salmon, Affleck, Nicolson, & Stewart, 2019).

In a review of UK prescribing practices and screening and monitoring of depression by UK dermatologists, Daunton, et al., (2019) created and administered a detailed survey featuring a range of low-, medium- and higher-risk clinical scenarios, designed to capture a snapshot of current dermatological practice in monitoring for depression with isotretinoin. Respondents indicated a wide variability in their approach, with a substantial proportion referring patients on to Psychiatry. Few dermatologists appreciated the importance of behaviours suggesting impaired impulse control (Daunton, Oyebo, & Goulding, 2019). The authors highlight that in the UK, waiting times for a consultation with a psychiatrist are lengthy, with 25% of respondents in their survey reporting that referred patients had to wait longer than 3 months. Appropriate screening and more frequent monitoring of symptoms in the dermatology clinic could instead be recommended. This does not require specialist training and could be accomplished by administering the Patient Health Questionnaire (PHQ)-9 or similar validated indices, both at baseline and at intervals.

Anecdotal experience and responses received from stakeholders in the call for information suggests there is wide variability among dermatologists in seeking a psychiatric opinion for patients prior to commencing isotretinoin. Although such referrals are sometimes justified, unnecessary referrals can lead to delay, expense and patient distress. Current British guidelines on isotretinoin prescribing were created without the input of a psychiatrist, and do not provide any guidance on what to do for patients with current or previous depression.

A recent service audit of isotretinoin prescribing in primary care in the UK concluded that the community dermatology service model provides a safe and efficient system for isotretinoin prescribing and monitoring. The community dermatology service has been prescribing isotretinoin at multiple locations in the UK for over 10 years. This is a consultant-led service that has been operating across multiple sites since 2007. General practitioners with a specialist interest (GPwSIs)<sup>34</sup> and dermatology specialist nurses conduct clinics. Isotretinoin prescribing is done by GPwSIs and there is regular and open access to discuss any challenging cases with the consultant, in addition to multidisciplinary team clinics every month. Prescribing via this route is proposed to provide care closer to home with shorter waiting times, more access at a variety of locations in the community. In addition, with the software system used, it is possible to have totally inclusive data for isotretinoin. This improves governance and allows for more robust auditing.

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<sup>34</sup> In 2015, the Royal College of General Practitioners (RCGP) agreed that the term GPwSI should be replaced by the term GP with Extended Role (GPwER). The RCGP defines a GP with Extended Role (GPwER) as a GP with a UK licence to practise, who is maintaining a primary care medical role, but undertaking an activity that is beyond the scope of general practice and requires further training. (Guidance and competences to support the accreditation of GPs with Extended Roles (GPwERs) in Dermatology (including Skin Surgery), Royal College of General Practitioners, 2019)

A recent audit of the service was carried out on all patients who were prescribed isotretinoin over a year from March 2017 to March 2018 (n=339). The 2012 BAD audit proforma was used, including the additional questions re complaints, litigation and clinical setting. The audit results included all 339 patients seen in the service for isotretinoin over the year. There were 204 female patients and 135 male patients. There were documented pregnancy tests for 199 (98%) on every contact. Fasting blood tests were done at baseline, first month and then once during treatment for 334 (99%). A depression screen was carried out at every contact for 327 (96%) patients (Gupta & O'Shea, 2020).

#### **4.3.8. Knowledge and awareness of isotretinoin risks**

Review of patients' knowledge and awareness of isotretinoin use and safety was undertaken in Saudi Arabia via non-interventional cross-sectional survey. Acne is highly prevalent among the young population in this country. A total of 105 patients with acne participated in the study, 77.1% were female and 22.9% were male, 88.6% knew about isotretinoin and its use and adverse effects. About (10.5%) of the participants used isotretinoin with mild acne which is contra to the recommended guidelines.

Nearly 56.2% of the participants did not examine blood glucose before isotretinoin use, 9.5% of the participants did not examine blood glucose, lipid profile or liver enzymes before isotretinoin use. Not all of participants knew that depression (40%), inflammatory bowel disease (79%), osteoporosis (54.3%), and sunburns (22.9%) are isotretinoin-associated risks. Most participants (89.5%) appropriately recognised teratogenicity as the greatest hazard concomitant with the use of isotretinoin. Despite that, 29.5% of the women did not know that they must stop administration of the drug at least 1 month before pregnancy. Half of participants (50.5%) did not know that they should not donate blood during use of isotretinoin and (61.9%) did not know they must stop administration of the drug at least 1 month before donation.

This study shows that patients with acne may not be sufficiently aware of the requirements for isotretinoin use. Therefore, greater attention should be given to educating physicians and pharmacists to improve the safe use of isotretinoin. The authors recommend applying more effective regulations to restrict non-prescribed isotretinoin dispensing in Saudi Arabia (Imam, Abdel-Sattar, Aldajani, Alsultan, & Aldajani, 2021).

Although this study indicated a lack of awareness of the risks of isotretinoin, it was conducted in Saudi Arabia and the differences in clinical practice may not be directly generalisable to the UK. However, formal studies have not been conducted in other countries to verify levels of awareness and this remains a concern raised by patients and their families.

#### **4.3.9. Psychiatric risk when used for conditions outside licensed indication**

A phase 1 clinical trial was conducted to evaluate the safety and preliminary efficacy of combining the oral histone deacetylase (HDAC) inhibitor vorinostat and isotretinoin in patients with advanced renal cell carcinoma (RCC). Vorinostat was administered at 300 mg orally twice daily in combination with escalating doses of isotretinoin for 3 consecutive days per week. A standard 3 plus 3 dose escalation design was used. Dose limiting toxicities were assessed during the first cycle to determine the maximum tolerated dose. Of 14 patients enrolled on the trial, 12 were evaluable for toxicity (6 cohort 1; 3 cohort 2; 3 cohort 3) and 11 for tumour response. One patient in cohort 1 experienced a dose limiting toxicity (grade 3 depression). Common grade 1–2 toxicities included fatigue and gastrointestinal effects (nausea, diarrhoea, anorexia). Maximum tolerated dose was established as vorinostat 300 mg with isotretinoin 0.5 mg/kg twice daily 3 days per week (Molina, et al., 2020).

A national UK audit evaluated medical management of hidradenitis suppurativa (N=55). Isotretinoin was offered to 11 patients (20%), 6 of whom also had acne, and clarithromycin to one (Haebich & El-



Dars, 2020), (Hasan & Ingram, 2020) demonstrating a reduction in the use of isotretinoin and regular screening of patients for depression.

De Almeida, et al., (2020) describe the occurrence of major depressive disorder in a 19 year old male undergoing isotretinoin treatment at 20mg daily for 1 year for pityriasis rubra pilaris, a rare chronic papulosquamous disease of unknown aetiology.

#### 4.4. Age restrictions

Questions on the benefit-risk balance of isotretinoin in adolescents have been raised by patients and family members, both in the call for information and Yellow Card reports. Some stakeholders feel the psychiatric risks outweigh the benefits in adolescents and that treatment should only be available for adults.

*'This drug should not be prescribed to children under 18. Adolescence brings hormonal imbalances resulting in mood swings which mean that those suffering and their carers are unable to identify psychiatric issues as they arise.'*

*Comment received through call for information*

Assessing the benefit risk in different age ranges of adolescents is difficult since:

- the initial clinical studies were not powered to identify these risks by age range
- data stratified by age was not routinely provided in periodic safety update reports
- breakdown of usage data by age range in the UK is currently unavailable.

In 2003, isotretinoin was the subject of a significant European procedure, covering consideration of all data relevant to the assessment of the risk-benefit ratio; as a result very considerable changes were made to European SmPCs (including for the UK). The procedure harmonised the SmPC for all isotretinoin medicinal products throughout the EU. In relation to use by adolescents, the newly harmonised SmPC clearly specified the indicated lower age limit for the drug as 12 years. This defined age limit had previously been absent from the UK SmPC. Also, a statement that the musculoskeletal side effect of back pain was common and particularly so in adolescent patients was added to Section 4.8 of the SmPC.

In the 2007 a review of paediatric data from Roche, demonstrated that age had no effect upon the kinetics of isotretinoin or its major metabolites and suggested that isotretinoin is similarly efficacious in patients under 18 years. The clinical efficacy data were derived from a subgroup analysis with a total of 300 Roaccutane-treated patients (103 patients aged 13 to 17 years and 197 adult patients) for periods of 16 to 20 weeks in the efficacy trial NR15645. However, the data do not allow an assessment of efficacy in different subgroups by age in patients aged 12 to 18 years.

During a European assessment of paediatric data in 2007 the pharmacokinetics of isotretinoin were explored by a two-compartment model built using data from four studies. The pharmacokinetics of isotretinoin and its three metabolites were comparable in paediatric patients aged 12 to 18 years and adult patients following single or multiple dose administration. The pharmacokinetics of isotretinoin were not dependent on patient age.

With regard to the safety information from the clinical trials, comparative data between adults and those aged younger than 18 years are limited, but the safety profile in paediatric patients appeared similar to that observed in adult patients in terms of adverse events and laboratory abnormalities.



The clinical safety data was pooled from the clinical trials into which patients aged younger than 18 years were recruited. Patients who received at least one dose of study medication were included in the safety cohort. The paediatric safety cohort comprised a total of 358 patients aged younger than 18 years of age. A safety cohort of 216 adult patients were generated from the same clinical trials (excluding the bone density study, which only recruited patients aged younger than 18 years) for the purposes of comparison.

In addition, the paediatric cohort was subdivided into 3 differing age cohorts; those aged 13 to 14 years (n=60), those aged 14 to 15 years (n=147), and those aged 16 to 17 years (n=151). Mean age was 15.1 years and median age 15.0 years. Within the 12 to 13 years subgroup, mean age was 12.8 years and median age 13 years. Safety data in children was limited particularly for those aged 12 to 13 years. Breakdown of safety data occurring at a frequency of >5% was provided by age cohort, with the commonest adverse events reported across all age groups being mucocutaneous, followed by back pain, epistaxis, arthralgia and headache. No psychiatric adverse reactions were reported in any age group at a frequency >5%. Details on adverse events accruing at a frequency <5% were not provided by age cohort.

Two patients (1%) from the paediatric group suffered from suicidal ideation (although no details are available on which paediatric sub-group these cases fell into).

The paediatric and adult groups received similar mean cumulative doses of isotretinoin (9260 mg versus 9052 mg). This translated to a mean weight adjusted dose of 136.7 mg/kg for the paediatric cohort and 125.6 mg/kg for the adult cohort; the mean body weight in the paediatric and adult groups being 67.75 kg and 72.09 kg respectively. 92% of the paediatric cohort and 83% of adults received at least 16 weeks of treatment. 55% of the paediatric cohort and 58% of adults completed 20 weeks of treatment.

Comparative data are limited but on the basis of those available, the safety profile in paediatric patients appears similar to that observed in adult patients in terms of adverse events and laboratory abnormalities. With regard to the age subgroups in the paediatric cohort, the small cohort sizes make it difficult to make any conclusions about the differences in adverse event profile between the age groups. This limits the conclusions which could be drawn on safety of use of isotretinoin in this age category.

In addition to clinical trial data submitted by Roche, the 2007 European review also reviewed all serious and non-serious events from both clinical trials and from spontaneous suspected adverse reaction reporting between 01/11/2001 and 31/05/2004 where the patients age was stated to be <18 years. 2173 reports were retrieved, stratified by separate system organ class for serious events and for non-serious events. Of these, 2114 reports related to the age group 13 to 17 years and 59 reports were for the group aged younger than 13 years.

For the 13 to 17 years cohort, the most frequently reported serious adverse events were psychiatric in nature. Depression accounted for 19% of the serious events in this cohort, suicide attempt 6%, suicidal ideation 4.4% and suicide 4.2%.

For the younger than 13 year old cohort, the highest proportion of serious adverse events were in the psychiatric class and were similar in quality to those in the older cohort – depression and suicidal ideation being prominent (including 2 non-serious cases of depression plus 1 suicidal ideation and 1 suicide attempt).

Withdrawal rates from trials of those aged older than 18 years were double that of those aged younger than 18 years, but the small cohort sizes make it difficult to make any conclusions between the age groups.

The conclusion of the Europe wide review in 2007 was that the risk-benefit assessment was considered to be positive, at that time, for isotretinoin in people aged 12 years and older. With regard to serious adverse events, the absolute numbers of events were considered too small at that time to draw any conclusions from the data.

Although the clinical efficacy has been demonstrated in 12 to 18 year olds, there remained some gap in the data on clinical safety in the 12 to 13 year old age group and potentially beyond, with small numbers included in the initial clinical studies.

There is also a gap in the literature regarding safety of isotretinoin and risk of psychiatric conditions in the paediatric and adolescent age groups. In the comprehensive systematic review and meta-analysis by Li, et al., (2019) examining use of isotretinoin and risk of depression in patients with acne, only one of the 21 studies included had a mean age between 12 to 19 years, one further study had a mean age of 19 years with the remaining being in the 20's (Li, et al., 2019). Considering adolescence is the peak age of acne and isotretinoin treatment, a more representative age group would be expected in the literature. The 12 to 14 year old age group appears to be particularly underrepresented in the paediatric clinical trials and literature.

Many young adults in the call for information highlighted that they were unaware of the psychiatric risks associated with isotretinoin or were too young at the time of isotretinoin initiation to comprehend the magnitude of these risks.

*'They sold the benefits to me like a drug dealer in the street and didn't think to mention the psychiatric and sexual side effects. They were so bad I didn't even know what was happening to me until friends and family started to ask what was going on with me and we had to figure it out.'*

*Comment received through call for information*

Many outlined that if the risks were communicated more effectively, they likely would not have initiated the treatment. People aged 16 years or older are entitled to consent to their own treatment. This can only be overruled in exceptional circumstances. Like adults, young people (aged 16 or 17 years) are presumed to have sufficient capacity to decide on their own medical treatment, unless there is significant evidence to suggest otherwise. In England

and Wales, children under the age of 16 years can consent to their own treatment if they are believed to have enough intelligence, competence and understanding to fully appreciate what is involved in their treatment (Gillick competent). However, there are many reports from individuals and families who believe the adolescents treated were not of sufficient maturity to understand the nature and implications of the proposed treatment. This might also include ability to recognise and verbalise changes in mood or feelings and thoughts and seek appropriate and timely help from family or healthcare professionals. These concerns might become less significant as the adolescent's age increases.

From the views of stakeholders and the review of the clinical trial and spontaneous data in the paediatric population, the question arises as to whether the benefit-risk balance of isotretinoin may differ between age groups taking into account potential maturity issues mentioned above. It could

be argued that in the absence of robust clinical trial data in very young adolescents, restrictions may be justified.

As age of onset of acne is generally from 12 to 13 years, consideration was given to restricting isotretinoin to older adolescents as a cautious approach to minimise serious side effects in younger adolescents who may still be vulnerable in terms of neurological, cognitive and skeletal immaturity until more robust safety data is available in this age group. In line with NICE guidance (NICE, 2021), isotretinoin is third-line treatment, meaning there is likely to be some time before appearance of acne, at a severe enough stage and after other interventions or therapies have been undertaken, to reach the clinical point where isotretinoin use is considered. However any consideration of age restriction needed to take into account that the risk of scarring increases with the severity and duration of acne.

#### 4.5. Further research

Further research is needed on the relationship between isotretinoin and psychiatric side effects to establish mechanism, risk factors, frequency, early signs, possible treatments and reversibility. Research is still needed into the mechanism of psychiatric side effects with isotretinoin, including exploring the dose-dependent relationship, and genetic susceptibility to better understand how these events may be avoided or mitigated.

*'I think if I were to suggest anything, it would be research into the long term potential side effects ie whether there is any risk to long term mental health and sexual health dysfunction, or long term effects on tendons, ligaments etc'*

*Comment received through call for information*

Well designed, blinded, randomised controlled trials would be required to provide scientifically sound, evidence-based data on this safety concern. However, this is logistically difficult due to practical (blinding) considerations given the superior efficacy of oral isotretinoin in the treatment of acne and its range of side effects and in the case of some psychiatric events, such as suicide, due to potential ethical concerns associated with using suicide as a study end point (McGrath, Gilson, Darvay, & Hickey, 2010).

The FDA recommended such studies in 2000 but in 2002 concluded it would be difficult to adequately blind because of the dry skin side effects of isotretinoin. Suggestions include using as a control topical isotretinoin, which dries the skin but has minimal absorption into the bloodstream, may overcome this issue (Bremner, 2012). However, a feasibility study, conducted in a single centre in Cairns, Australia, found that one-third of eligible patients declined to participate as they did not want to delay treatment with isotretinoin (Rea, Tucker, Frittekki, & Gunnarson, 2018).

It has previously been estimated that it would take a prospective study of at least 8000 patients to comprehensively assess the possible psychiatric adverse effects of isotretinoin (Goodfield, et al., 2010). In the absence of such a definitive study, there will remain a degree of legitimate uncertainty as to its safety in patients with current or pre-existing depression.

Further safety data is required, stratified by age, including adolescent age cohorts, to review benefit-risk by age group.

One approach for gathering large amounts of real-world data would be through the establishment of an isotretinoin drug registry. This would be an extremely useful tool for investigating psychiatric events, particularly suicidality and psychosis, as it would allow collection of detailed information

regarding all events experienced, dates, dose, duration of treatment and other medications or medical conditions that could be risk factors or confounders. It would also allow the sequence of events to be studied and potential prodromes or triggers for psychiatric events to be identified.

In the absence of this further research, or until such tools can be put in place, the focus needs to be on educating patients and their families about psychiatric side effects with isotretinoin, considering prescribing lower doses, using the shortest possible treatment courses, pre-screening and monitoring for psychiatric events and having appropriate management plans for patients who experience psychiatric side effects, including onward referral to a specialist where necessary.

#### 4.6. Discussion

Responses to the call for information and the presentations provided by stakeholders made clear the devastating impact of severe psychiatric side effects, some of which were long term, in patients taking isotretinoin.

Establishing a causal association between a medicine and a possible side effect can be difficult, particularly if the effect is also associated with other factors such as the underlying condition being treated.

The data currently available do not allow a firm conclusion to be drawn on why isotretinoin appears to increase the risk of severe psychiatric side effects in some patients and not in others. Mechanisms have been identified by which isotretinoin can theoretically lead to psychiatric side effects. Studies provide conflicting evidence with some showing an improvement in mental health when skin improves and others showing treatment-emergent psychiatric side effects. Population based studies overall do not demonstrate an increased risk, however, this may be due to improvements in underlying psychiatric conditions for some individuals nullifying the increased incidence of isotretinoin induced side effects in others.

Underlying genetic predisposition may have a part to play and some evidence has been found for a specific genetic marker to be associated with an increased risk of depression in response to isotretinoin treatment (Alzoubi, et al., 2013). Further research is required to better understand the reasons for the differences in risk of psychiatric side effects in individual patients.

As a dose-dependent effect has been noted in the clinical development programme and in terms of side effects, isotretinoin should be prescribed at the lowest effective dose. Many healthcare professionals who responded to the call for information outlined how they had not seen psychiatric side effects in their patients, which they attributed to only using low doses.

*'I have used low dose isotretinoin for thousands of patients. The results have been overwhelmingly positive. With low doses e.g. 20mg or 30mg daily few adverse events are experienced. With low doses psychiatric side effects are very low. I would emphasize the importance of ease of access to the GP or dermatologist in the event of a psychiatric side effect.'*

*Comment received through call for information*

Similarly, some report that in patients with a personal or family history of psychiatric disorders, their use of lower dose regimes has ensured patients do not have a relapse or onset of new psychiatric symptoms. Larger randomised controlled trials of low-dose and intermittent-dose regimes incorporating psychiatric monitoring throughout study, in both adults and adolescents, would be beneficial to establish if these treatment routines offer benefit over the current indicated posology. The committee for the NICE acne guideline noted, in the recently updated guidance,

that evidence for lower dose oral isotretinoin was scarce, and therefore this was prioritised as one of the key recommendations for research.

Questions on the benefits and risks of isotretinoin in adolescents has been raised by patients and family members, both in the call for information and Yellow Card reports. Some stakeholders feel the psychiatric risks outweigh the benefits in adolescents and that treatment should only be available for adults. Adolescence and puberty may be considered a time of psychiatric vulnerability, with isotretinoin potentially adding to this risk. However, increased sebum production in puberty and development of nodular cystic acne during this time can result in significant scarring. Therefore, the benefit of isotretinoin treatment remains of significant importance as last line treatment.

Review of the clinical trial data and literature in adolescents reveals a gap in data in the younger adolescent age group. In the absence of robust data, it may be proportionate to implement further prescribing restrictions until such a time that the benefit-risk balance can be reviewed by age group. Any delay in isotretinoin initiation needs to be balanced against the risk of permanent scarring, which carries its own risk in terms of mental wellbeing and quality of life.

There is limited information on the long-term safety of isotretinoin and the continuation of adverse effects after treatment has finished from the clinical development programme and subsequent paediatric trials. This is due to lack of systematic data collection on psychiatric side effects and short follow-up periods. There have been a significant number of reports of continuation of adverse events in both the Yellow Card data and the call for information. This is often distressing for individuals and can have a significant impact of quality of life. Further research is required in this area to establish mechanisms, understand reversibility of adverse events and define treatment options.

There appears to be much variation around the information provided to patients regarding the potential for psychiatric adverse effects with isotretinoin. Improvements to the product information and accompanying materials could be made by including further guidance about appropriate mental health screening, monitoring and follow-up tools (for depression, suicidality and psychosis) and providing more tailored and comprehensive advice about the possibility of psychiatric reactions and the prodromal symptoms that patients and their families should be alerted to so that early intervention can be implemented. More information on dose, screening, monitoring and follow-up of individuals with underlying psychiatric conditions or family history of psychiatric conditions should be considered to ensure access and safe treatment where the benefit-risk balance is considered positive. Consideration should be given as to how information could be made available to patients prior to the first dermatology visit to give time for comprehension of all the risks and discussion with family where appropriate.

Beyond the regulatory remit, education and targeted information provision for healthcare professionals involved in isotretinoin treatment and management of individuals may be beneficial.

*'It helped us hugely psychologically to have the treatment and get rid of acne. The dryness does not impact sexual activities. The acne caused me years of misery. I am happy I avoided that to my daughter by being able to get the treatment for her early. Years of acne is traumatic. The skin scars for life are traumatic. The patients need to be provided the treatment quicker to optimise it. My daughter had it as a teenage and only needed one course. I had it in my 30s and needed 2 courses.'*

*Comment received through call for information*

This would address the mixed views expressed by healthcare professionals on a possible association between isotretinoin and psychiatric disorders and also address the stark variation in information relayed to patients on this potential risk.

The consensus from recent UK literature is that screening and monitoring in this group could be accomplished by administering the Patient Health Questionnaire (PHQ)-9 and Hospital Anxiety and Depression Scale or General Anxiety Disorder 7-Item (GAD-7) scale, both at baseline and at intervals throughout treatment. Similarly, many healthcare professionals who submitted to the call for information suggested screening and monitoring via standardised questionnaires (such as PHQ-9) would be a proportionate risk minimisation measure. Dermatologists should be supported to feel comfortable administering standard validated indices in clinic, both to screen for depression at the outset and to monitor mood while patients are being treated with isotretinoin.

Regular psychiatric monitoring is also being proposed in other territories, such as in the USA where monthly iPLEDGE<sup>35</sup> visits have been identified as providing an opportunity to screen patients for psychiatric conditions and improve outcomes.

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<sup>35</sup> [iPledge REMS - Public Home Page \(iplodgeprogram.com\)](https://www.fda.gov/oc/ohrt/iplodge-program)

## 5. SEXUAL DYSFUNCTION

This chapter summarises the available information considered by the Isotretinoin EWG on sexual dysfunction suspected to be associated with isotretinoin including data from literature and spontaneous reports and information from stakeholders.

The Isotretinoin EWG was asked to consider whether further regulatory action was required to minimise the risk of sexual dysfunction suspected to be associated with isotretinoin and whether further research is required to better characterise the risk of sexual disorders suspected to be associated with isotretinoin and to evaluate the long term impact.

### 5.1. Sexual function and dysfunction

#### 5.1.1. Sexual health and functioning

Sexual activity is important for humans not only for reproduction, but also for socialisation, bonding and pleasure. A healthy sex life has been shown to have many benefits on mental and physical health.<sup>36</sup> The National Institute of Clinical Excellence (NICE) in their report on the impact of sexual health<sup>37</sup> state that: *'Sexual health is an integral part of overall health, well-being and quality of life.'*

NICE in their Clinical Knowledge Summary (CKS) on Erectile Dysfunction<sup>38</sup> report that erectile dysfunction can affect the physical, emotional and psychosocial health of the sufferer. Complications include:

- Anxiety
- Depression
- Lack of sexual confidence
- Low self-esteem
- Interpersonal difficulties
- Relationship difficulties
- Impaired quality of life of the sufferer and that of their partner and family

The situation is complicated further by the fact that mental health issues can themselves have a negative or inhibitory effect on sexual functioning, and many antidepressant medications may also be associated with sexual dysfunction.

The sexual response cycle refers to the sequence of normal physical and emotional changes that occur as a person becomes aroused and participates in sexual activities, including intercourse and masturbation<sup>39</sup>. There are four phases to the sexual response cycle: desire (libido), arousal (excitement), orgasm and resolution.

#### 5.1.2. Sexual Dysfunction

Sexual dysfunction refers to an issue affecting any phase of the sexual response cycle that prevents the individual or couple from experiencing satisfaction from the sexual activity<sup>40</sup>.

Sexual dysfunction can be classified in many ways, but a helpful method uses the categories of the sexual response cycle:

Desire disorders – lack of sexual desire or interest in sex

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<sup>36</sup> <https://www.healthline.com/health/healthy-sex-health-benefits>

<sup>37</sup> [Overview | Acne vulgaris: management | Guidance | NICE](#)

<sup>38</sup> <https://cks.nice.org.uk/topics/erectile-dysfunction/>

<sup>39</sup> <https://my.clevelandclinic.org/health/articles/9119-sexual-response-cycle>

<sup>40</sup> <https://my.clevelandclinic.org/health/diseases/9121-sexual-dysfunction>



- Arousal disorders – inability to become physically aroused or excited during sexual activity
- Orgasm disorders – delay or absence of orgasm
- Pain disorders – pain during intercourse

Sexual response and satisfaction involves a complex system. Dysfunction can manifest in a variety of different ways in both men and women. The end result of sexual dysfunction will generally involve elements of dissatisfaction, upset, stress, embarrassment and shame.

## 5.2. Summary of information from stakeholders via call for information

There were 278 responses to the call for information which included information pertaining to sexual dysfunction with isotretinoin. The majority of these came from individuals, where just under half had negative opinions. Over a third of individuals providing information on sexual dysfunction had positive opinions on isotretinoin overall.

Individuals with positive opinions had generally experienced improvements in their acne and resulting quality of life. They had generally not suffered serious side effects. However, some patients remained positive about isotretinoin treatment despite having side effects including sexual side effects.

*'It has made my day to day life much better. Although there has been some side effects, these effects do not stop me leaving the house, whereas acne did.'*

*Comment received through call for information*

Individuals with negative opinions were more likely to have suffered sexual side effects with isotretinoin that were considered significant or persistent or both. They voiced the embarrassment, distress, and anxiety this had caused them, and in some cases was still causing them.

Many individuals explained how they were too embarrassed to raise their sexual issues with their prescriber, or they were concerned that isotretinoin would be stopped when all they wanted was to be rid of their acne.

*'As a female I developed dyspareunia that because of it's psychological impact is hard to overcome. That alone caused me more pain (and for longer) than any pain I might have suffered from having acne into adulthood.'*

*Comment received through call for information*

*'Isotretinoin induced persistent sexual side effect, like total loss of libido and erectile dysfunction. Side effects didn't resolve after discontinuation of isotretinoin.'*

*Comment received through call for information*

*'Most men are too embarrassed to admit that they can't get an erection, this side effect has also been under reported because of this.'*

*Comment received through call for information*

There were some individuals who highlighted that they were too young to fully appreciate their sexual dysfunction at the time of their isotretinoin therapy, and they described the difficulties of maturing sexually whilst suffering with sexual dysfunction. Many did not appreciate the extent of their problems until they started to engage in sexual activities with partners. They generally did not



know of a link between isotretinoin and certain types of sexual dysfunction and would never have suspected their medication might be responsible.

*'By its very nature, it conceals itself. Think about it: a 13-, 14- or 15-year-old boy or girl, barely pubescent, suddenly is struck with sexual dysfunction. This poor young soul hasn't had much of a chance to understand what healthy sexuality looks and feels like.'*

*Comment received through call for information*

Sexual dysfunction is recognised to have possible negative effects on self-esteem and mental health and intimate relationships. In some cases, this had repercussions on all aspects of people's lives. Several expressed concerns about not being able to settle down with a partner or have children because they were unable to perform sexually. Those who responded generally felt that they had not been warned about sexual side effects and had not been properly counselled or monitored.

Some individuals would have received isotretinoin at a time when the link with erectile dysfunction, vulvovaginal dryness and reduced libido, was not known and there were no warnings in the product information, so they could not have been warned. However, there was frustration amongst some individuals that they were not believed when they raised concerns about sexual side effects with isotretinoin.

Individuals also raised concerns about how their sexual dysfunction had been managed

*'It also ruined a long-term relationship I had in the beginning where both of us had thought we would get married. It has disappointed countless other potential partners since, and it has generally left me on the sidelines of life in the sense of that I had been looking forward to having children and not doing so has left me unable to relate to friends and peers...'*

*Comment received through call for information*

*'Patients should definitely be informed about the sexual risks. this risk is great. Because adolescents who have just discovered their functions will not notice the disorders.'*

*Comment received through call for information*

including lack of appropriate services and treatments, especially for those where symptoms had not resolved after stopping and had continued long term.

Friends and families of patients who had experienced sexual dysfunction with isotretinoin also responded to the call for information. They made up around 10% of the responses that

mentioned sexual side effects and generally their overall views of isotretinoin treatment were negative. The accounts of friends and families highlighted the impact on intimate relationships and family relationships. They described the anger patients can feel towards parents who they think should have protected them from isotretinoin. Parents explained they were trying to act in their children's best interests with the information that was made available to them at the time, but several expressed regret and extreme guilt at encouraging their children to take isotretinoin. The outcome for some had been a total breakdown in family relationships.

*'If a patient asks their dermatologist about these effects, as I did myself, they are met with an immediate shutdown of any possibility that these symptoms will last, let alone even exist in the first place.'*

*Comment received through call for information*

*'He blames us, his parents, for taking the risks involved with this drug. We were the adults, he was the child. We feel dreadful - guilty, depressed, stupid....My poor son is impotent as a result of a terrible decision made by his parents. He is depressed and sad and angry, and his relationship with us, his parents, is broken.'*

*Comment received through call for information*

Some friends and relatives have had to deal with psychiatric side effects in their loved ones including suicide. The anguish and heartache felt by families and friends affected by these issues was profoundly expressed in contributions to the call for information. The accounts received gave an insight into the difficulties patients and their families had faced and illustrated how long lasting the consequences could be.

Patients and their friends and families generally asked that the risk of sexual dysfunction with isotretinoin is better communicated to patients, including a warning that issues may continue long-term. Many suggested patients should be monitored for these side effects. There were suggestions about whether restricting isotretinoin to people older than 18 years might be of benefit. However the data so far had not allowed conclusions to be drawn regarding whether age presented a risk factor. Postponing treatment must be balanced against the risk of acne scarring (which carries its own risks of psychiatric effects), and the possible need for longer courses and higher doses when treatment is delayed.

*'...has had a devastating effect on our family. He has a younger sister and brother, who have along with us have had to deal with aftermath of grief and deal with suicide being the reason.'*

*Comment received through call for information*

Healthcare professionals provided approximately one-fifth of the 278 responses that included information on sexual dysfunction. The vast majority of these had positive views on isotretinoin. The positive views were based largely on how effective isotretinoin is at treating acne, and how this has such a positive impact on patient's lives.

*'I have not really come across sexual disorders in pts on isotretinoin though confess I don't tend to ask and perhaps we need guidance on what to ask about and if any pts are at increased risk of sexual disorder on the tablet.'*

*Comment received through call for information*

Most healthcare professionals stated they had not seen sexual side effects with isotretinoin, although several of these admitted that they did not usually ask about it. Encouragingly, many had said they had started to ask about these side effects recently.

Some healthcare professionals suggested that they had not seen patients with sexual side effects because they only ever used low doses of isotretinoin.

Many healthcare professionals expressed that they needed more information on sexual side effects, including how to prevent it and manage it, and better access to sexual health services for patients who are struggling with sexual dysfunction.

### 5.3. Yellow Card Reports

Cumulatively, there were a total of 184 Yellow Cards for isotretinoin that included one or more terms pertaining to sexual side effects at the data lock point of 20 May 2021.

### 5.3.1. Age and gender

In 80% of the reports, the patient was identified as male and 19% as female. In the remainder the gender was unknown. A valid age was provided for 160 of the 184 patients reporting sexual dysfunction. Age information is presented in table 2.

A valid age was provided for 160 of the 184 patients reporting sexual dysfunction. Age information is presented in table 2.

Table 2. Age of patients reporting sexual dysfunction with isotretinoin on Yellow Cards

|                                  | All patients   | Male patients | Female patients |
|----------------------------------|----------------|---------------|-----------------|
| <b>Number</b>                    | 184*           | 147           | 35              |
| <b>Number (%) with valid age</b> | 160 ** (87.0%) | 128 (80.0%)   | 31 (19.4%)      |
| <b>Age range</b>                 | 14 – 50 yrs    | 14 – 50 yrs   | 16 – 42 yrs     |
| <b>Median age</b>                | 21 yrs         | 21 yrs        | 26.0 yrs        |
| <b>Average age</b>               | 23.0 yrs       | 22.2 yrs      | 26.0 yrs        |

\*Note for 2 patients gender was not reported.

\*\* 1 person of unknown gender was reported to be 22 years old.

Age has presented a challenge for this review, in that some patients gave their age when they started isotretinoin, others reported their age when they suffered a side effect and some have provided their age at the time of their report, and this could be many years after their treatment. It was not always possible to tell which of these options for age had been provided, so it is difficult to draw conclusions about age, and whether any particular age groups are especially at risk.

From the information on age provided, female patients reporting sexual side effects appear to be older than male patients. This could reflect female individuals being offered and trying contraceptive pills prior to starting isotretinoin and the use of contraception may have a confounding effect on libido. However, as some aspects of female sexual dysfunction may be less immediately obvious and possibly more subjective, girls and women also may not appreciate they have an issue until they are older.

### 5.3.2. Dose

It is difficult to identify a relationship between sexual side effects and dose of isotretinoin for several reasons. Firstly, the dose of isotretinoin was not always reported by patients submitting Yellow Cards.

The product information recommends a starting dose of 0.5mg/kg daily with a dose range of 0.5 to 1.0mg/kg per day. In the Yellow Cards, patients' weights have generally not been provided, so it is not possible to identify if patients were taking the recommended dose for their weight.

The dose of isotretinoin is usually titrated up or down according to response and side effects, so patients may have taken different doses throughout their treatment course. Where a single dose has been provided on a Yellow Card, it was not usually possible to decipher if that represented the initial dose, the final dose or the dose that the patient was taking when they experienced a side effect. It was often not possible to identify the dose the patient was taking at the time of any sexual side effects, and some patients continued with their isotretinoin treatment despite experiencing side effects.

For 73 patients of the 184 who reported sexual side effects, some information about dose of isotretinoin was provided. Table 3 shows the number and percentage within each dose range.

Table 3. Dose of isotretinoin provided by 73 of the 184 patients reporting sexual dysfunction

| Daily dose    | No. of patients | Percentage of patients with dose provided (n=73) |
|---------------|-----------------|--|
| 20mg or under | 15              | 20.6%  |
| 21 – 40mg     | 33              | 45.2%  |
| 41 – 60mg     | 16              | 21.9%  |
| 61 – 80mg     | 9               | 12.3%  |

Table 3 shows that doses are spread as may be expected for a drug that is titrated according to body weight, response and tolerability, with the majority of patients reporting mid-range doses.

Unfortunately, without details of the patient’s weight it is not possible to establish whether the doses are above the recommended 1 mg per kg body weight or could be classified as high doses.

Given the heterogeneity of the data on dose, no firm conclusions can be made on the relationship between dose and sexual dysfunction.

As mentioned above in the call for information (section 5.2), several healthcare professionals, stated that they had not seen sexual side effects and felt this was due to only using low doses of isotretinoin.

The product information states that long-term remission and relapse rates are more closely related to the total dose administered than to either duration of treatment or daily dose, with no substantial additional benefit expected beyond a cumulative treatment dose of 120 to 150 mg/kg. The product information advises that a treatment course of 16 to 24 weeks is normally sufficient to achieve remission from acne.

The data available on dose from the Yellow Cards was not sufficiently robust to draw firm conclusions, but there were reports of patients taking doses above 60 mg which as a 1 mg/kg dose, may be considered high for some patients, especially younger patients. A fifth of patients with dose information provided (21.9%), received a dose between 41 and 60 mg of isotretinoin.

### 5.3.3. Confounding factors

The majority of Yellow Cards reporting sexual side effects with isotretinoin provided no information about co-morbidities or concomitant medications, but given their generally young age, this was not surprising.

A minority of patients reported conditions and medications that may have impacted their sexual function. The most obvious of these were mental health conditions with associated use of antidepressants and antipsychotics. The complex relationship between sexual dysfunction, mental health and treatments for mental health is explored further below.

Another potential confounding factor that could not be explored through Yellow Card data is the influence of alcohol and illicit drugs on both mental health and sexual functioning.

### 5.3.4. Types of sexual side effects reported

The following is an analysis of the individual types of sexual side effects that have been reported with isotretinoin. A single Yellow Card may contain several sexual side effect terms, and therefore could be included in the analyses below more than once.

### 5.3.4.1 Erectile dysfunction

Overall, in the Yellow Card database there were 93 cases of erectile dysfunction (ED) with isotretinoin. This represented 50.5% of all cases reporting sexual side effects (93/184) and 63.2% of male patients reporting sexual dysfunction (93/147).

*‘Since starting the treatment i now have issues getting/maintaining an erection. This never happened before starting my treatment, and I’m not sure exactly how long into my treatment i noticed the issue as it was gradual.’*

*Comment received through call for information*

The numbers and percentages for erectile dysfunction need to be taken in the context that spontaneous reporting systems are inherently prone to under-reporting, but when the side effect in question is highly personal and a cause of embarrassment, the extent of under-reporting is likely to be increased. It can be assumed that the true number of patients experiencing erectile dysfunction with isotretinoin is likely to be higher than what has been reported via the Yellow Card scheme.

Reports of erectile dysfunction did not always have full information regarding isotretinoin dose, treatment start and stop dates and erectile dysfunction start and stop dates. It is therefore very difficult to draw conclusions on how dose and treatment duration contribute to this side effect. The missing data also makes it challenging to identify a pattern of erectile dysfunction with isotretinoin in terms of how quickly it is likely to occur and the effect of dose reduction or dose cessation. The fact that some men did not experience symptoms until after drug cessation further complicates the role of dose and treatment duration.

Where information on time to event is available, this time might include time for the man to notice the side effect and make a connection with the drug, and time for them to feel comfortable with disclosing it. Isotretinoin is commonly used in adolescents who may not be fully sexually active, and it may have taken time for them to become fully aware of their issues.

From the information in the Yellow Card database, it appears that erectile dysfunction can occur days, weeks or months after starting isotretinoin, and in a few cases, it did not occur until after stopping isotretinoin treatment. The majority of men reporting erectile dysfunction appeared to have experienced it within the first month of starting isotretinoin.

Where information was provided, half of men reported their erectile dysfunction did not stop when they stopped their isotretinoin. There are reports of men continuing with these symptoms for up to 24 years. Table 4 shows the number of years erectile dysfunction had persisted for in those men where the duration of time had been reported.

Table 4. Number of years erectile dysfunction (ED) has persisted for after stopping isotretinoin where this was reported (27 patients)

| Length of Time ED had been going on for at the time of reporting | No. of males |
|--|--------------|
| Less than 1 year   | 5            |
| 1 – 2 years  | 3            |
| 2 – 3 years  | 2            |
| 3 – 4 years  | 3            |
| 4 – 5 years  | 1            |
| 5 – 6 years  | 1            |
| 6 – 7 years  | 1            |
| 7 – 8 years  | 2            |

|                      |   |
|----------------------|---|
| <b>8 – 9 years</b>   | 2 |
| <b>9 – 10 years</b>  | 0 |
| <b>10 – 11 years</b> | 0 |
| <b>11 – 12 years</b> | 1 |
| <b>12 – 13 years</b> | 1 |
| <b>13 – 14 years</b> | 2 |
| <b>17 years</b>      | 1 |
| <b>21 years</b>      | 1 |
| <b>24 years</b>      | 1 |

Erectile dysfunction is generally difficult to conceal and could make even the act of having sex challenging or impossible. This is likely to have a very significant impact on self-confidence and relationships and may lead to avoidance of intimacy altogether. Amongst men experiencing erectile dysfunction with isotretinoin, there is evidence of depression, anxiety and suicidality. This may be anticipated to be worse where symptoms have continued long term or there appears to be no hope of improvement. Psychiatric side effects in patients reporting sexual side effects with isotretinoin are considered further below.

#### 5.3.4.2 Reduced Libido

Cumulatively, 74 Yellow Cards have been received reporting issues with libido (sex drive and interest in sexual activities). This represents 40.2% of the Yellow Cards reporting sexual side effects with isotretinoin. All but one of these reports related to loss of or a reduction in libido. One report described libido increasing.

Reduced libido is listed as a side effect in the product information for isotretinoin, but the frequency is unknown. In the Yellow Card database, libido issues were the second most common type of sexual dysfunction reported with isotretinoin.

Reduced libido was reported in patients across a wide age range from 14 to 49 years. Dose was frequently not provided or was difficult to interpret due to increasing and decreasing doses, and therefore it is not clear what dose of isotretinoin the patient was taking at the time of they experienced the side effect. Where information was available, it appeared patients taking a variety of doses of isotretinoin have reported reduced libido.

*‘As a healthy 16 year old male, I had strong sexual urges, which were severely diminished during that time of treatment and it stayed that way for at least a year. Getting an erection was hard and my sexual passion was silenced.’*

*Comment received through call for information*

Treatment duration was not always provided. Many patients completed the recommended 4 to 6 months of isotretinoin treatment but there was evidence of some patients who reported reduced libido stopping their treatment earlier than expected, and this may have been due to the side effects. The majority of the men reporting reduced libido, also reported erectile dysfunction.

The time it took for the reduced libido to occur was frequently not reported. From the information available, onset occurred days, weeks or months after starting therapy with isotretinoin or in a few cases not until after isotretinoin had been stopped. It appears most patients were aware of this symptom within weeks to months of starting isotretinoin.

Around half of patients reporting reduced libido reported that it did not improve on stopping isotretinoin. In some patients the symptoms have persisted for years including up to 25 years.

### 5.3.4.3 Other events of sexual dysfunction

#### 5.3.4.3.1 *Vulvovaginal dryness*

There were 10 reports of vulvovaginal dryness in the Yellow Card database. Of these 10 reports, 4 had failed to resolve with stopping isotretinoin and symptoms continued to be a problem months to years later. One patient was still struggling with her symptoms 6.5 years after stopping. In addition to these cases, there was one report of dyspareunia (painful intercourse) in a woman who was reported to have had changes to the vaginal mucosa that mimicked atrophic vaginitis. It was not reported whether isotretinoin was stopped, but the side effect was said to be resolving.

*'The drug caused me to suffer from vaginal dryness and I had to start using lubrication firstly during sex then also daily because the dryness started causing pain. It made a big difference to my sexual pleasure and I often couldn't climax, or it would take a much longer time, which was never a problem before. Sex was still enjoyable but I found it frustrating and quite upsetting that I couldn't fully enjoy my sex life.'*

*Comment received through call for information*

#### 5.3.4.3.2 *Genital hypoaesthesia*

There were 7 Yellow Card reports (3 involving male and 4 involving female), reporting genital hypoaesthesia (reduced sensation in the genitals).

*'I am rarely able to climax... I am unable to use a condom due to insensitivity.'*

*Comment received through call for information*

For 2 of the male patients, symptoms of genital hypoaesthesia were still persisting 7 and 11 years after stopping isotretinoin. In one male patient, the symptoms had improved with sequelae at 7 years. Of the female patients, 2 still had symptoms 5 months and 10 months after stopping isotretinoin.

#### 5.3.4.3.3 *Orgasm difficulties*

There were 6 Yellow Cards reporting difficulties with orgasm. There was one report of orgasmic sensation decreased in a male patient and 5 reports of anorgasmia (lack of orgasm) in one male patient and 4 female patients.

In 5 of these cases, the orgasm difficulties persisted despite stopping isotretinoin. For one female patient, the effect had not resolved 19 years after stopping isotretinoin, and another female patient continued to suffer effects 6 years after stopping isotretinoin. For one of the male patients, symptoms were ongoing after 11 years and another reported to still have symptoms 9 years after starting therapy.

*'Mechanically, I can have an orgasm, but there is no mental pleasure and everything feels kind of numb and disconnected.'*

*Comment received through call for information*

#### 5.3.4.3.4 *Ejaculation disorder*

There were 5 reports of ejaculation disorder with isotretinoin. These included 2 reports of difficulty with ejaculation with no further details provided. The first occurred in a 20 year old and did not

recover at the time of reporting the side effect, the other was in a 27 year old after 3 months of treatment, and it was not reported if the symptoms recovered after isotretinoin was stopped.

A watery, thin ejaculate was reported by one male who was aged 23 years. This resolved 2 months after stopping isotretinoin.

Ejaculatory failure was reported with no further details in a 28 year old male within a week of starting isotretinoin. The symptom persisted but treatment was ongoing at the time the report was submitted and no further information is available.

In another case of ejaculatory failure, a male of unknown age gave no details on the symptoms, but reported they were recovering after isotretinoin was withdrawn.

Isotretinoin is known to reduce secretions from certain types of epithelium, and a literature report is discussed in section 5.4.1 that highlighted the reduction in seminal fluid experienced by one male patient taking isotretinoin.

#### 5.3.4.3.5 *Premature Ejaculation*

Two reports have been received of premature ejaculation. Neither give any further details regarding the onset, duration or recovery of these side effects.

#### 5.3.4.3.6 *Sexual Dysfunction*

There have been 24 reports of sexual dysfunction with isotretinoin. These relate to 21 male individuals, 2 female individuals and 1 person of unknown gender.

*'Isotretinoin has completely decimated my sexual function. I now have difficulty getting and maintaining an erection, deal with premature ejaculation, have diminished pleasure during orgasm, and overall low libido.'*

*Comment received through call for information*

In 9 of the male cases, sexual dysfunction included erectile dysfunction, and 4 of these also had reduced libido. There was one man who reported sexual dysfunction with reduced libido, and in another male sexual dysfunction included orgasmic sensation decreased. The 2 female patients both reported sexual dysfunction with loss of libido and anorgasmia, but one of them also had genital hypoaesthesia.

### 5.3.5. **Patterns of sexual dysfunction symptoms**

Healy, et al., (2018), describe a syndrome of enduring sexual dysfunction with isotretinoin consisting of loss of function, loss of libido and genital anaesthesia. (See published literature in section 5.4 for further details). There are low numbers of patients in the Yellow Card database who have reported symptoms consistent with the syndrome of enduring sexual dysfunction with isotretinoin that has been described by Healy, et al. However, there are patients who appear to have experienced this phenomenon and for the majority of these, the symptoms have continued long term.

Within the Yellow Card reports for sexual dysfunction with isotretinoin, 3 male patients reported erectile dysfunction, reduced libido and genital anaesthesia or reduced sexual sensation. For one male patient, symptoms partially recovered after stopping isotretinoin, although reduced sexual sensation remained. For the other 2 male patients, symptoms continued for 7 years and 11 years after stopping isotretinoin treatment. The last male patient had an additional side effect of anorgasmia.



Yellow Cards for 3 women with vulvovaginal dryness, reduced libido and genital anaesthesia. Symptoms were persistent for all women and were ongoing at 5 months, 9 months and 6.5 years after stopping treatment.

Yellow Cards for 2 women reported reduced libido, genital anaesthesia and anorgasmia. In one of these women symptoms appeared to have been ongoing for 1 year at the time of reporting (approximately 9 months after stopping isotretinoin), and in the other woman symptoms were ongoing 6 years after stopping isotretinoin.

In one woman anorgasmia, loss of libido and a vulval disorder related to the appearance of her genitals were reported. Symptoms had persisted for approximately 16 months at the time of reporting and this was over a year after stopping isotretinoin.

### 5.3.6. Psychiatric side effects in isotretinoin patients reporting sexual dysfunction

Psychiatric side effects including depression, anxiety and suicide are listed in the product information for isotretinoin and are discussed further in section 4 of this report. Depression and anxiety can be associated with sexual dysfunction, but conversely, having sexual dysfunction is upsetting and distressing and could itself cause anxiety and depression. The risk may be especially high if sexual dysfunction occurs at an age when people are first gaining confidence and experimenting with their sexuality, or where symptoms are persistent. Depression and anxiety can themselves lead to suicidality, but the impact of sexual dysfunction on intimate relationships, especially where symptoms continue long term can also contribute to poor mental health.

Amongst the 184 Yellow Cards reporting sexual side effects with isotretinoin, 54 (29.3%) also included side effects such as depression, anxiety, suicidal behaviour, or suicide. Of these 54 patients, 46 (85%) were male, 6 were female and in 2 cases gender was unknown. For comparison, 80% of patients reporting sexual side effects with isotretinoin overall were male.

Table 5 shows the cumulative totals of depression, anxiety and suicidality amongst patients reporting sexual dysfunction with isotretinoin, with some patients reporting more than one of these events.

Table 5. Depression, Anxiety and Suicidality amongst patients reporting sexual dysfunction with isotretinoin (n=184)

| Psychiatric event | Number (%) of patients |
|-------------------|------------------------|
| Depression        | 41 (22.3%)             |
| Anxiety           | 24 (13.0%)             |
| Suicidal Ideation | 26 (14.1%)             |
| Suicide attempt   | 4 (2.2%)               |
| Deaths by suicide | 6 (3.3%)               |

Table 5 shows that depression, anxiety and suicidal ideation were commonly reported alongside sexual side effects with isotretinoin. It must be noted that in many cases it was not possible to identify whether sexual side effects predated the psychiatric side effects, or vice versa. It was also not usually possible to identify if anything else may have contributed to the sexual side effects or the psychiatric side effects, for example acne itself, other medical conditions, medications, alcohol or illicit drug use. However, there are cases where it is explicitly stated that sexual dysfunction occurred, with no other explanation than isotretinoin, and that it was the sexual dysfunction that triggered depression, anxiety or suicidality.

Amongst the patients reporting sexual and psychiatric side effects with isotretinoin, there were 26 patients with suicidal ideation and 4 patients who attempted suicide. There were also 6 suicides. The suicides occurred in 5 male patients and 1 patient of unknown gender. One of the reports involving a

male patient cited difficulties with the opposite sex as part of the issue that led to the suicide. For the other cases, there was insufficient information to conclude whether suicide was a direct result of sexual dysfunction. The 6 suicides generally reported unspecified sexual dysfunction, or loss of libido.

Of the 54 patients reporting a combination of sexual and psychiatric side effects with isotretinoin, it was unknown whether the sexual side effects had resolved in 20 patients. Of the 34 patients where an outcome for sexual side effects had been provided, 28 (82.4%) reported that their sexual side effects had not recovered or not resolved at the time the Yellow Card was submitted. Only 3 patients reported that their sexual side effects had recovered.

Of the 26 patients with suicidal ideation, 11 had not provided outcome details for the sexual side effects reported. Where details had been provided, 1 had recovered and 14 had not recovered or not resolved at the time the Yellow Card report was submitted. Of the 4 cases reporting suicide attempts, 3 reported that their sexual side effects had not recovered or not resolved, and for the 6 suicides, 1 case of unspecified sexual dysfunction was reported to have not recovered, but in the other 5 cases the outcome of the sexual side effects was not known.

Given that sexual side effects may be embarrassing and distressing to report, it is not known how many patients with psychiatric side effects with isotretinoin may have also experienced sexual side effects. Cases are further complicated by the fact that both acne and isotretinoin are associated with psychiatric issues, and both psychiatric issues and their treatments can cause sexual dysfunction.

#### **5.4. Published literature**

The literature surrounding isotretinoin and possible sexual side effects is not extensive. The general themes of available literature are discussed below.

##### **5.4.1. Sexual Dysfunction with Isotretinoin**

###### **5.4.1.1 Enduring sexual dysfunction / Triad of sexual side effects**

Two papers discuss the possibility of enduring sexual dysfunction with isotretinoin and both use data from the RxISK online database (Hogan, et al., 2014), (Healy, et al., 2018).

The first of the papers involving data from the RxISK database by Hogan, et al., (2014), aimed to describe cases of enduring or persistent sexual dysfunction with SSRIs, finasteride and isotretinoin. The authors had noticed similarities between the sexual dysfunction events reported for these 3 drugs. In the RxISK database, 7 cases of enduring sexual dysfunction with isotretinoin were identified. The length of time that constituted 'enduring' does not appear to have been defined. All of the 7 cases with isotretinoin were men, and all had erectile dysfunction. In 6 of the 7 cases loss of libido and in 3 cases genital anaesthesia were also reported. There was one case each for orgasm difficulties and ejaculation problems.

Hogan, et al., indicate that they have noticed that SSRIs, finasteride and isotretinoin appear to be associated with a triad of sexual dysfunction symptoms. The triad consists of genital anaesthesia, loss of libido and loss of function (for example, anorgasmia, erectile dysfunction in males, vulvovaginal dryness or loss of lubrication in women). Time to onset could be as early as 30 minutes for genital anaesthesia after initiating treatment with an SSRI, but in some cases the problem only emerged after medication was stopped. The authors postulate that the mechanism for sexual dysfunction may be linked to epigenetic changes, as a hormonal explanation could not explain the persistence of the effects. The authors discuss the severe consequences of enduring / persistent sexual dysfunction including the risk of suicide.

The second paper to examine enduring or persistent sexual dysfunction in the RxISK database is by Healy, et al., (2018), and considers cases of persistent sexual dysfunction with SSRIs, finasteride and isotretinoin.

Healy, et al., (2018) report 300 cases of enduring sexual dysfunction related to drugs including SSRIs, finasteride and isotretinoin. Again, there does not appear to be an explanation of what length of time met the definition 'enduring'. Isotretinoin had the most reports with 49 male cases and 5 female cases, and it is assumed that this number includes the cases in the previous paper by Hogan, et al.,. For the 49 male cases, events included erectile dysfunction (46), loss of libido (35) and genital anaesthesia (18). The 5 women suffered loss of libido (5), genital anaesthesia (3) and difficulty achieving orgasm (2).

Healy, et al., (2018) highlights a triad of sexual symptoms with isotretinoin, SSRIs and finasteride pertaining to loss of libido, genital anaesthesia and loss of function. They also discuss the persistence of symptoms and consider this to be a 'legacy syndrome' which they report is particularly seen with isotretinoin. Within the RxISK database, 8 isotretinoin patients had ongoing sexual symptoms 10 years after stopping and 4 patients continued to have symptoms 20 years after stopping.

Healy, et al., (2018) raise concerns about symptoms not presenting until after medication has stopped, or symptoms getting significantly worse after medication stopped. They state there were 9 cases with isotretinoin, where sexual dysfunction first appeared or became significantly worse, only after therapy was stopped. The authors label this 'tardive sexual syndrome'. They compare it to the tardive dyskinesia experienced by some patients taking antipsychotics, which also may not present or worsen until after therapy stops.

Isotretinoin is a drug that will be stopped abruptly, however Healy, et al., (2018) points out that tapering dose with SSRIs does not prevent enduring sexual dysfunction from occurring with those medicines.

Healy, et al., (2018) are not clear if the effects are neurological or endocrinological or whether they occur peripherally or centrally. They speculate that the effects may occur due to epigenetic changes to receptors or ion channels. This aspect is considered further in section 3 of this report.

Healy, et al., (2018) highlight the impact of enduring or persistent sexual dysfunction on the lives of those affected. They report that within the 300 cases of enduring sexual dysfunction with SSRIs, finasteride or isotretinoin in their database, 25 relationships broke up including 9 marriages. Work was reported to be difficult for 90 people and 12 people lost their jobs. Healy, et al., (2018) do not break down these numbers by drug taken, so the proportion who were taking SSRIs (where anxiety and depression may have contributed to events) is not provided.

#### 5.4.1.2 Erectile dysfunction

Tirado Sanchez, et al., (2005) describe 6 men suffering erectile dysfunction in a trial to evaluate the efficacy and safety of isotretinoin in acne. This was published before product information was updated to include erectile dysfunction, but the author's suggestion that further study is warranted remains valid, given that the relationship between erectile dysfunction and isotretinoin and mental health remains not fully understood.

#### 5.4.1.3 Effects on ejaculation

A case report from Coleman, et al., (1994), discusses a 29 year old man who developed an inability to ejaculate following isotretinoin treatment for acne. The man was usually highly sexually active (intercourse 10 times per week) and found after one week of isotretinoin he could only ejaculate every fourth or fifth time he had sexual intercourse. After 2 weeks of treatment despite continuing to engage in sexual activity, he could only ejaculate every 2 weeks. The author discusses how a

failure to ejaculate could be due to neurological dysfunction or from a reduction in the volume of seminal fluid. 80% of seminal fluid is produced from the seminal vesicles and the seminal vesicles are lined by pseudostratified columnar epithelium containing goblet cells. Isotretinoin is known to affect this type of epithelium reducing secretions from goblet cells resulting in dryness for example of the mouth and nose. The author proposes that the cause of the man's ejaculatory failure was from isotretinoin-induced reduction in seminal fluid, through effects on the goblet cells of the seminal vesicles. Given that this man was particularly sexually active, he may have noticed the effect more than men who have less frequent sexual activity. The patient recovered completely 5 days after stopping treatment with isotretinoin.

#### 5.4.1.4 General sexual dysfunction

A systematic review by Zakhem, et al., (2019), included 2 isotretinoin studies (both already discussed above), and 3 acitretin case reports, (Reynolds, 1991), (Rossi & Pellegrino, 2009), (Halkier-Sorensen, 1988) including one with erectile dysfunction and positive rechallenge (Reynolds, 1991). This provides evidence of sexual dysfunction that has been experienced with isotretinoin, although it provided very few cases overall. Zakhem, et al., (2019) raises the point that patients are often hesitant to seek help for these issues and may not suspect medications to be the underlying cause of their symptoms. They stress the importance of dermatologists being aware of these potential risks, and they encourage conversations about it with their patients. Zakhem, et al., (2019) advise actively screening all patients for sexual adverse effects, especially those with pre-existing risk factors.

#### 5.4.1.5 Mucocutaneous side effects affecting the genital and perianal skin

A letter to the editor of the Journal of American Academic Dermatology from Cunningham, et al., (2020) looked at side effects affecting the skin of the genitals and perianal areas. It is well known that isotretinoin dries out the skin and commonly causes cheilitis and xerosis, but genital or perianal dermatitis, fissures and bleeding may not be warned about or expected. Cunningham, et al. performed a questionnaire-based study of 80 patients over the age of 16, with a minimum of 3 months of treatment.

Of the 50 women surveyed, there were 16 reports of vulval dryness (32%), 11 for vulval discomfort (22%), 10 with dyspareunia (20%) with avoidance of intercourse in 8 of these women, 5 vulval fissures (10%), and 12 reporting new or increased need for lubricating agents (24%). In the overall cohort, 16 out of 80 reported perianal dermatitis (20%), 21 reported fissures (26%) and 16 reported perianal bleeding (20%).

Cunningham, et al., (2020) discuss that adverse effects such as dermatitis, fissures and bleeding affecting the genital and perianal skin appear to be common with isotretinoin in practice, but they are uncommonly reported in the literature. Consequently, these effects may not be pointed out to patients by clinicians. This study highlights that patients do not voluntarily report these symptoms, and there is a need to include preventative and management advice to all patients.

In Yellow Cards and the call for information responses, there was evidence of patients reporting sexual dysfunction secondary to physical skin changes affecting their genital and perianal areas. These effects can cause sex to be uncomfortable, painful or physically difficult.

#### 5.4.1.6 Male Fertility

Cinar, et al., (2016), examined sperm samples and blood hormone levels from 81 men before and after a 6 month treatment course of isotretinoin for severe or refractory acne. Results showed that after 6 months of isotretinoin treatment all parameters on the spermogram improved including sperm concentration, total progressive motility, total progressive motile sperm, normal morphology

and vitality and the improvements were statistically significant. There was no statistically significant change in blood values including total and free testosterone, LH or FSH.

Amory, et al., (2017), hypothesised that as vitamin A deficiency is known to reduce sperm production, isotretinoin (as a synthetic vitamin A analogue), might improve sperm count and restore fertility. They studied 19 men between the ages of 21 and 60 years with infertility (for longer than 12 months) associated with low sperm concentrations of below 15 million sperm/ml. Sperm samples and blood samples were taken at baseline to confirm the low sperm count, and then every 4 weeks during isotretinoin therapy and until 24 weeks after therapy stopped. The results showed a significant increase in sperm concentration from baseline to the end. There was no significant change in sperm motility but there was a trend towards improved sperm morphology. Partners of men in the cohort had 6 pregnancies (3 spontaneous and 3 assisted), which resulted in 5 live births (including 1 set of twins). All the spontaneous pregnancies and 4 of the births overall, occurred in men who had improved sperm count. The authors conclude that isotretinoin can improve sperm count and result in improved fertility, but the numbers included are small. The authors did not report on the effects on blood serum hormone levels.

#### 5.4.1.7 Female fertility

Aksoy, et al., (2015), found that ovarian reserve (as shown by measurement of AFC, AMH, OV and sex hormones) was significantly decreased in 82 women at the end of 6 months of systemic isotretinoin therapy. This implied that isotretinoin has a negative effect on female fertility. However, it is acknowledged that women with low ovarian reserve can still fall pregnant, and women with high ovarian reserve might still suffer infertility.

A subsequent study by Cinar, et al., (2017) aimed to investigate the long-term effects on female fertility by re-evaluating patients from the Aksoy study, 12 months after the 6 month course of isotretinoin. Of the 82 women in the original study, 79 could be contacted and agreed to partake in this follow up study. All women were reviewed at 18 months after starting isotretinoin (12 months after finishing a 6 month course) and underwent pelvic ultrasound and blood tests on day 2 to 5 of their menstrual cycle. The results showed that mean total OV, total AFC and mean AMH, which had all decreased at the end of 6 months, had all returned to normal at the eighteenth month. The increases between month 6 and month 18 were all significant. There were no significant changes in serum LH or FSH and the change in oestradiol was not significant. All were lower than pre-treatment levels. Testosterone levels increased significantly between 6 and 18 months but remained lower than pre-treatment levels. Cinar, et al., (2017) conclude that although isotretinoin has a negative effect on ovarian reserve, the effects appear to be reversed at 12 months after stopping isotretinoin. They propose the mechanism is a direct toxic effect of isotretinoin on the ovary which recovers after cessation of the drug.

Ozturk, et al., (2015) also investigated ovarian reserve in 32 women treated with isotretinoin. Blood tests (including hormone levels) were measured on day 2 to 4 of the menstrual cycle, before isotretinoin treatment and monthly during treatment. Pelvic ultrasound was performed to measure parameters of ovarian reserve in the first 2 to 4 days of the menstrual cycle both before and after treatment. Duration of isotretinoin treatment ranged from 5 to 8 months. Following treatment FSH, LH and estradiol levels were significantly lower compared with pre-treatment levels. AFC and OV also decreased, but the change was not significant. Ozturk, et al., (2015) discuss the mechanism for effects on the ovary, and they propose it may be due to retinoic acid inhibition of cell proliferation and induction of apoptosis (programmed cell death). There is discussion of whether this might be mediated by transcription factor Forkhead box O1 (FoxO1). It is postulated that the reductions in pituitary hormones and subsequently sex hormones, may also be related to FoxO1 suppression of genes. (See section 4 on mechanisms for isotretinoin action and adverse effects for further details).

Akturk, et al., (2014), performed a case control study looked at ovarian reserve in 22 women treated with isotretinoin compared to 22 women without treatment. They found that after treatment, the isotretinoin group had a significant reduction in AMH levels compared to the control group. They propose that the decreased levels of AMH levels may suggest isotretinoin has a detrimental effect on the ovaries. They discuss how isotretinoin affects various tissues in the body and is regarded as a pro-drug inducing apoptosis in cells. They describe how retinoic acid is isomerised to ATRA. Binding of ATRA to retinoic acid receptors initiates changes in the receptors affecting co-repressor and co-activator proteins, thus activating the transcription of primary target genes. Forkhead box class transcription factors are again implicated in pro-apoptotic signalling. The authors hypothesise that the decline in AMH levels may indicate that isotretinoin is associated with decreased numbers of granulosa cells because of isotretinoin's apoptotic effect on granulosa cells in the ovaries.

#### 5.4.1.8 Hormone levels

There is evidence that isotretinoin reduces testosterone levels. This would lead to an improvement in acne but may also be a possible mechanism for erectile dysfunction and reduced libido.

Karadag, et al. have performed several studies looking at the effect of isotretinoin on hormone levels. 2 previous studies showed significant drops in testosterone, LH, TSH, free T3, cortisol, ACTH and prolactin after 3 months of isotretinoin therapy. (Karadag, Ertugrul, Tural, & Akin, 2011), (Karadag, Ertugrul, Tural, & Akin, 2010). A further study aimed to investigate the effect on hormone levels of varying doses of isotretinoin (Karadag, et al., 2015). The authors recruited 105 patients with moderate to severe acne (75 female and 30 male patients). Mean age was 21.8 years.

Fasting blood samples were taken prior to isotretinoin treatment and 3 months later. Treatment continued for 6 months and was either continuous high dose (0.5 to 1mg/kg per day) continuous low dose (0.2 to 0.5 mg/kg per day) or intermittent high dose (0.5 to 1mg/kg per day), where treatment was only given for 1 week out of every month. After 3 months of treatment there were significant reductions in LH, prolactin, total testosterone, ACTH, cortisol, insulin-like growth factor binding protein, insulin like growth factor 1, growth hormone and free T3 for the whole group but this was most evident for the high dose group. Several results lacked significance for the intermittent group. Karadag, et al. conclude that isotretinoin affects pituitary hormones at all doses, but the differences were more pronounced for the high dose group. The weakest effect was for the intermittent treatment. The authors discuss how lower doses and intermittent doses of isotretinoin may reduce the effects on hormones and this may in turn reduce some adverse effects which may be mediated through these hormone changes. However, lower doses and intermittent doses, may mean the effect on acne is reduced.

#### 5.4.1.9 Polycystic Ovarian Syndrome

Acmaz, et al. investigated the effects of isotretinoin on women with PCOS (Acmaç, et al., 2019). The rationale was that some women cannot take the contraceptive pill, which is a standard treatment for PCOS, and isotretinoin could be a useful alternative for them. The study recruited 40 women with PCOS and acne who attended an outpatient clinic for treatment of their acne. All patients were ineligible for the oral contraceptive pill. Baseline bloods and pelvic ultrasound were performed prior to 6 months of isotretinoin treatment. Bloods and ultrasound were repeated after 6 months. The results showed that after 6 months of isotretinoin treatment, there were improvements in all objective measures of PCOS, including a significant reduction in free testosterone. The authors suggest the success may be due to the reduction in circulating testosterone, but they also postulate that isotretinoin might interfere with the expression of androgen receptors, meaning the effect of testosterone would be reduced.

### 5.4.2. Sexual dysfunction in young people

The National Survey of Sexual Attitudes and Lifestyles (Natsal)<sup>41</sup> is one of the largest and most comprehensive scientific studies of sexual behaviour and lifestyles in the world. It is a major source of data informing sexual and reproductive health policy in the UK. The survey has been carried out every 10 years since 1990 and has so far involved interviews with 45,000 people. The third survey, Natsal-3 took place in 2010 and included 15,162 men and women aged 16 to 74 years in Britain.

Data from Natsal-3 was used in a publication from 2016 by Mitchell, et al. which looked at sexual function in 16 to 21 year olds (Mitchell, et al., 2016). The authors analysed data from 1875 sexually active and 517 sexually inactive, participants aged 16 – 21 years.

In Natsal-3, participants were classified as sexually active if they reported vaginal, oral or anal sex with one or more partners in the past year. The sexually active participants were asked whether they had experienced any of a list of 8 difficulties with their sex life, lasting 3 months or longer in the past year. The 8 areas covered interest in sex, enjoyment, anxiety, pain, arousal, climax or orgasm, lubrication, erection. Where people admitted to a sexual problem, they were also asked to consider their level of distress at the problem.

Of the sexually active men aged 16 to 21 years (n=854), 33.8% had experienced one or more sexual function problem lasting 3 months or more in the last year. The sexual problem was reported to be distressing in 9.1%, implying that among men reporting one or more problem, just over a quarter (26.9%), felt distressed. The most commonly reported sexual function problem among young men was reaching a climax too quickly (13.2%), followed by lack of interest in sex (10.5%). Difficulty getting and keeping an erection was reported in 7.8%.

For sexually active women aged 16 to 21 years (n=1021), 44.4% experienced a sexual problem lasting 3 months or more in the last year. The sexual problem was reported to be distressing in 13.4%, implying of those reporting one or more problem, 30.2% were distressed. The most commonly reported sexual function problem in young women was lack of interest in sex (22.0%) and experiencing difficulty in reaching climax (21.3%). These were also the most common distressing problems, (5.3% and 6.3% respectively.)

It was reported that 35.5% of the young men and 42.3% of the young women who reported a problem had sought help, but rarely from professional sources. Family members and friends were the most common sources, followed by the media or self-help. Among participants who had not had sex in the last year, more than 10% of young men and women said they had avoided sex because of sexual difficulties.

The Mitchell, et al. study concludes that distressing sexual function problems are reported by a sizeable minority of sexually active people, (approximately 1 in 10 sexually active young men and 1 in 8 sexually active young women). They advise that given these figures, education is required, and counselling should be available, to prevent lack of knowledge, anxiety or shame contributing to the problem and potentially risking lifelong sexual problems.

In the Mitchell, et al. study, (based on the Natsal-3 data), the prevalence estimate for erectile difficulties (7.8%), is midway between the 4.3% found in an Australian study of sexually active 16 to 19 year olds (Richters, Grulich, de Visser, Smith, & Rissel, 2003) and the 11% of sexually active 16 to 24 years olds in a study from Portugal (Quinta Gomes & Nobre, 2014).

The prevalence estimates for young women regarding lack of interest (22%), and difficulty reaching orgasm (21.3%), are slightly lower than in the Australian study mentioned above (36.7% and 29%

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<sup>41</sup> <https://www.natsal.ac.uk/>

respectively), (Richters, et al., 2003) and comparable with rates of approximately 20% and 27% in a Swedish study of women aged 18 to 24 years (Obergh, Fugl-Meyer, & Fugl-Meyer, 2004).

A study by Moreau, et al. (2016) reported on a survey in 1484 young people aged 15 to 24 years in France. A telephone questionnaire asked about their sexual functioning over the past 12 months.

The 944 female respondents reported that they sometimes experienced the following: difficulty reaching orgasm (21%), lack of sexual desire (20%), pain during intercourse (18%), lack of pleasure during intercourse (14%), vaginal dryness (8%).

The following sexual events were reported to sometimes occur in the 731 male respondents: difficulty reaching orgasm (6%), lack of sexual desire (9%), pain during intercourse (5%), lack of pleasure during intercourse (6%), problem maintaining an erection (4%) and premature ejaculation (18%).

Despite suffering these sexual dysfunctions, 93% of female and 92% of male respondents reported that they were satisfied or very satisfied with their sex life. The authors state that this showed that although sexual dysfunctions appeared to be common, for many people such symptoms were not reported to be a problem for them.

O'Sullivan, et al. offer an explanation for this, in their study looking at prevalence and characteristics of sexual functioning in adolescents (O'Sullivan, Brotto, Byers, Majerovich, & Wuest, 2014). They suggest that a proportion of problems in young people arise from a lack of practice effect, and these will likely disappear over time as young people gain confidence and experience. In support of this, the study found that young men with a longer period of sexual experience had better erectile functioning and greater satisfaction with intercourse. The authors also highlight a proportion of adults reporting lifelong symptoms that first appeared at or before the time of their sexual debut and have not subsided.

O'Sullivan, et al. conclude that both male and female adolescents will at times experience sexual problems which are distressing. Highly distressing sexual problems occur in a substantial minority of adolescents. These findings highlight the need for young people to be provided with age appropriate information about how to deal with sexual problems when they do arise, to decrease their distress, and to ensure that these problems do not become entrenched.

In a review into erectile dysfunction by Rastrelli, et al. (2017) the authors comment that epidemiological studies consistently show that prevalence of erectile dysfunction increases with age, so that advancing age remains one of the most important unmodifiable risk factors for erectile dysfunction. However, they note that complaints of erectile dysfunction in younger men are becoming more and more frequent. They discuss how erectile dysfunction in younger men is likely to be overlooked and dismissed without performing any assessment, such as medical history or physical exam. This is often due to the widespread assumption that erectile dysfunction in younger individuals is a self-limiting condition that can be managed with patient reassurance alone. However, evidence shows that in younger subjects, organic, psychological and relational conditions can all contribute to the pathogenesis of erectile dysfunction. Young men with erectile dysfunction need to be evaluated for all of these conditions and treated as necessary.

#### **5.4.3. Influence of dose on sexual dysfunction with isotretinoin**

In the review by Zakhem, et al., it was proposed that dose reduction may ameliorate sexual dysfunction side effects with isotretinoin (Zakhem, et al., 2019). Whilst a dose-dependent response for isotretinoin and sexual dysfunction has not been formally established, the concept is plausible and logical. Some of the healthcare professionals who responded to the call for information, suggested that they had not seen sexual dysfunction with isotretinoin because they only used low doses.



In the letter to the editor of the Journal of American Academic Dermatology from Cunningham, et al. (2020) regarding adverse effects of genital and perianal skin from isotretinoin, a dose-dependent relationship was suggested, and higher doses were found to have higher risk. In their questionnaire based study of 80 patients over the age of 16 years, and with a minimum of 3 months of treatment, Cunningham, et al. found a causal association between higher daily doses of isotretinoin (higher than 50mg) and cumulative doses higher than 6000mg and incidence of vulval dryness, vulval fissures and perianal dermatitis. They also found an association between higher doses and perianal fissures and bleeding, but this was not true for cumulative doses.

In a paper by Abdelmaksoud, et al. (2020) it is postulated that the response to isotretinoin is in fact not dose-dependent. The authors' reasoning is that isotretinoin seems to exert its effects and adverse events through changes in genetic expression, and these could occur even with low-dose isotretinoin. They therefore question whether there is ever a need for high doses. Their review looks for evidence of safety and efficacy of low dose isotretinoin in various conditions.

With regard to treatment of acne, they quote a study from Yap that found 10mg as a fixed daily dose of isotretinoin was safe in long duration and effective in the management of acne (Yap, 2017) . They also mention a study by Dhaked, et al. (2016) which compared the response of moderate to severe acne in a fixed daily or alternate daily dose of 20mg of isotretinoin for 24 weeks. Both regimes were effective, but a daily dose of 20mg of isotretinoin was superior in terms of response. Finally, Faghihi, et al. (2017), showed in a clinical trial of 60 patients treated for 6 months, that low dose isotretinoin (0.25mg/kg per day) compared to 0.5mg/kg per day gave no significant difference in clinical improvement between the two groups, but there were fewer side effects with low dose isotretinoin.

Abdelmaksoud, et al. conclude that from the evidence they have seen, lower doses of isotretinoin do not increase relapse rate or side effects for a range of conditions including acne. However, they do not provide detail of the methodology used to conduct this review, and they give very little presentation of data and numbers.

The recently published NICE guideline on acne vulgaris management (June 2021)<sup>42</sup>, has made the following recommendations regarding dose of isotretinoin.

Isotretinoin should be prescribed at a standard daily dose of 0.5 to 1 mg/kg. They advise considering a reduced daily dose of isotretinoin (less than 0.5mg/kg), for people at increased risk of experiencing adverse effects. They state that the risk of adverse events is multifactorial, and so assessment of risk would be dependent on the person's circumstances and could not be quantified as part of the recommendation.

They suggest when giving isotretinoin as a course of treatment for acne:

- Continue until a total cumulative dose of 120 to 150mg/kg is reached, (the evidence showed that total cumulative doses of at least 120mg/kg in a single course were more effective compared with total cumulative doses lower than 120mg/kg in a single course)

but

- If there has been an adequate response and no new acne lesions for 4 to 8 weeks, consider discontinuing treatment sooner.

The committee for the NICE acne guideline noted that evidence for lower dose oral isotretinoin was scarce, and therefore this was prioritised as one of the key recommendations for research. The suggested research question was: What is the efficacy of reduced dose oral isotretinoin in the management of acne vulgaris?

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<sup>42</sup> [Overview | Acne vulgaris: management | Guidance | NICE](#)

## **5.5. Identifying and monitoring sexual side effects**

In the Yellow Cards and in the responses to the call for information, many reporters and respondents expressed frustration and concern about lack of monitoring for sexual side effects with isotretinoin. The most obvious way to assess and monitor this would be by way of a structured questionnaire administered at baseline (before treatment initiation), and at regular intervals during the treatment course. Self-administered questionnaires may be preferable to those administered by healthcare professionals, as they may avoid embarrassment or discomfort on both sides. However the healthcare professional would need to be confident and comfortable with discussing any issues that are raised.

A literature search identified a variety of reliable and validated questionnaires and rating scales to assess all aspects of sexual dysfunction, however, all had limitations for use in this context. A tool for monitoring for sexual dysfunction with isotretinoin would need to be something that healthcare professionals who are not experts in sexual functioning could quickly and easily use to screen all genders and a variety of ages within a dermatology setting. It would need to highlight issues within the major areas of the sexual response cycle, which then leads to further discussion of those issues and an appropriate management plan regarding isotretinoin and any need for referral to a specialist in sexual function.

So far, it has not been possible to identify risk factors for sexual dysfunction with isotretinoin. It would seem sensible however, to identify anyone with pre-existing sexual dysfunction in case isotretinoin has a worsening effect. A baseline sexual function questionnaire would therefore be useful. Given that it is not possible to predict which patients may suffer sexual dysfunction with isotretinoin, all patients should be monitored for these effects.

Consideration needs to be given on how the questionnaire should be administered to patients accompanied by parents or guardians, especially those who are younger than 18 years old. Young people may not want their family members present whilst they are filling out the questionnaire, and they may not wish them to see their answers. Although, some young people may be more open with their relatives.

## **5.6. Discussion**

The product information for isotretinoin currently lists erectile dysfunction, vulvovaginal dryness and reduced libido as possible side effects but does not include any information to indicate that these side effects may continue long term in some patients after treatment with isotretinoin has been stopped.

Information from Yellow Cards and other international regulators confirmed that sexual side effects do not appear to be commonly reported with isotretinoin. However, there is likely to be significant under reporting given how sensitive these issues are.

Information from Yellow Cards, the call for information responses and the presentations from stakeholders highlight that patients taking isotretinoin report a wide range of sexual side effects with isotretinoin which can continue long term, in some patients, and can have a devastating impact on patients and their families.

There was evidence of depression, anxiety, and suicidality (including suicide) amongst patients reporting sexual side effects with isotretinoin. Parents of those affected by sexual side effects with isotretinoin have expressed guilt and regret that they agreed to their child receiving prescriptions of isotretinoin. Patients who received isotretinoin as adolescents, who are now adults, express anger and resentment that their parents did not protect them.

Many patients taking isotretinoin are at a point where they are starting to experiment sexually either by themselves or with a partner. Evidence from the general population shows that sexual dysfunction is common amongst young people at this stage in their life<sup>43</sup>. Much of this will be self-limiting and will improve with confidence and experience. However, for a few people sexual dysfunction will persist throughout their lifetime. The challenge is identifying when sexual dysfunction is part of normal sexual development and the background risk in the population, and when it appears to be related to isotretinoin. There appears to be a range of ages affected by this issue, including people aged older than 18 years.

Any delay in isotretinoin prescription needs to be balanced against the risk of permanent scarring which carries its own risk in terms of mental wellbeing and quality of life. Consideration is also needed with regard to the adolescent's ability to participate in a meaningful way in conversations around potential risks as well as any risk minimisation measures including questionnaires.

In terms of dose, it is postulated that sexual side effects with isotretinoin may be dose-dependent. This is plausible but has not been formally demonstrated.

The literature surrounding isotretinoin and sexual side effects is limited and further research is clearly needed. An isotretinoin drug registry may be a suitable way of gathering further data. The registry could help establish risk factors for sexual dysfunction, early signs, possible treatments and reversibility. Data are also needed on the complex relationship between psychiatric events and sexual dysfunction, especially identifying possible sequences of events.

In the interim, patients being considered for treatment with isotretinoin need to be warned about the possibility of sexual side effects and monitored. In Yellow Cards and the responses to the call for information, many patients expressed frustration at the lack of warnings and monitoring they received.

Monitoring for sexual side effects with isotretinoin could take place via a self-administered questionnaire. Ideally this will be quick and easy to administer to all patients and cover general sexual dysfunction to act as a screening test.

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<sup>43</sup> <https://www.natsal.ac.uk/natsal-survey/natsal-3>

## **6. OVERVIEW OF KEY THEMES IDENTIFIED**

This chapter provides an overview of the overarching issues identified in the course of the review by the Isotretinoin EWG, including those raised by patients and their families.

### **6.1. Data limitations**

Limitations in the available data mean that it is difficult to definitively establish causal associations with either the psychiatric or sexual side effects suspected to be associated with the use of isotretinoin. However, an association could not be ruled out and the individual experiences of patients and families continue to raise concern.

### **6.2. Better information on side effects to support informed decision making**

A significant proportion of patients and stakeholders, including those with both positive and negative views on isotretinoin, agreed that further action was needed to raise awareness of the possible risks associated with isotretinoin and that this should not be limited to the risks of psychiatric and sexual side effects. Clear and consistent messaging should be used to explain the risks to patients and their families, in order for patients to make an informed decision about treatment with isotretinoin.

Patients and stakeholders highlighted the need for trusted information about isotretinoin that the patient had time to consider, prior to making a decision about treatment with isotretinoin.

The Patient Information Leaflet for isotretinoin currently contains extensive information. However, the patient only receives the leaflet with the medicine after isotretinoin has been dispensed and the decision to use it has been made. The format of the Patient Information Leaflet was considered by the Isotretinoin EWG to not be optimal, but the format is defined within medicines legislation and therefore there were limitations to the changes that could be made. However, additional educational materials could be developed, with input from stakeholders, to be provided to patients in advance of prescribing decisions that was more accessible than the Patient Information Leaflet.

### **6.3. Frequency of psychiatric side effects**

Patients and stakeholders have raised concerns about the frequency of psychiatric side effects as presented in the SmPC, given that they were less than the background rate of psychiatric side effects in the general population and therefore could be interpreted as falsely reassuring to healthcare professionals and patients. It was noted that the frequencies of psychiatric side effects were based on spontaneous reporting rates and that more robust data on which to base expressions of frequency were lacking. However, the additional educational material could include information to help patients to understand the uncertainty in this risk and its likely order of magnitude.

### **6.4. Awareness of the risk of side effects continuing long term**

Patients and stakeholders raised concerns regarding the occurrence and/or persistence of side effects after treatment with isotretinoin had stopped. The product information currently includes a general statement warning that some side effects may continue but this does not indicate which side effects are prolonged or for how long.

Patients and stakeholders felt strongly that the possibility of side effects continuing long term must be explained to patients. Particularly when those side effects have the potential to have a greater impact than their acne.

## **6.5. Screening and monitoring of patients**

Although the product information recommends that patients should be monitored for psychiatric disorders, the method of monitoring is not defined. Many patients and stakeholders recommended systematic screening and monitoring of psychiatric disorders. There are various existing tools and questionnaires available and these were considered by the Isotretinoin EWG and the CHM.

The product information does not currently provide any guidance regarding monitoring for sexual side effects and it was suggested by patients and stakeholders that this needed to be addressed.

## **6.6. Further restriction of use of isotretinoin**

Some stakeholders raised concerns about the balance of risks and benefits of isotretinoin treatment and called for it to be banned completely or its use restricted.

The use of isotretinoin in the UK is currently restricted in a number of ways. It can only be prescribed by specialists, which is interpreted to mean a consultant dermatologist in the UK. The majority of isotretinoin is dispensed from hospital pharmacies by pharmacists experienced with isotretinoin and particularly the risks for female patients if they become pregnant.

There have also been concerns raised that isotretinoin is prescribed for milder forms of acne which could argue for greater oversight of new prescriptions.

Any restrictions must be balanced against the many positive life-changing experiences reported and the theme of improving mental health and confidence after effectively treating acne.

## **6.7. Restriction of use of isotretinoin based on age**

There were calls from some patients and stakeholders for the use of isotretinoin to be restricted in adolescents. Currently, it is advised that isotretinoin should not be used for the treatment of prepubertal acne and is not recommended in children younger than 12 years of age due to a lack of data on efficacy and safety. Concerns were raised that adolescents may be more susceptible to side effects as their bodies and brains are still developing. There were also concerns that adolescents may not fully comprehend the risks prior to treatment.

Acne is more common in young men during adolescence, but in adulthood, incidence is higher in women. It has been reported that acne is one of the most common skin conditions in the UK leading to 3.5 million visits to primary care every year (Dawson, 2013).

It is difficult to estimate usage of isotretinoin in the UK and no data is available on the age of patients receiving treatment.

The assessment of psychiatric and sexual side effects has included assessment of age where this information has been provided. These cover wide age ranges with the mean age generally in the 20s.

## **6.8. Access to treatment and subsequent support**

Some patients highlighted difficulties and delays in accessing treatment with isotretinoin because of both the regulatory restrictions currently in place and dermatology resources. There are concerns about the damage associated with those delays both to scarring of the skin and on mental health if treatment is delayed. This must be taken into consideration in relation to possible restrictions on use.

## **6.9. Informed decision making**

Some stakeholders called for the introduction of formal written consent prior to starting isotretinoin to verify that the risks have been fully discussed with the patient and understood.

In the UK, issues of consent for medical treatment are defined by clinical practice and the General Medical Council. However, the educational materials currently include an acknowledgement of risk form for female patients and their prescribers to sign to confirm they understand the risks associated with the use of isotretinoin during pregnancy. The educational materials could be updated to incorporate a form which covers other isotretinoin risks which could be used for all patients.

## **6.10. Dosing guidance**

Many of the side effects of isotretinoin are recognised to be dose-dependent and the dosing recommendations are individualised based on the patient's weight, with a dose range depending on the patient's response and tolerance.

Specific dosing regimens are not always clear in spontaneous case reports and there have been suggestions that lower doses may be associated with lower risks but there is limited efficacy data for these alternate dosing regimens and not all side effects are dose related.

## **6.11. Clinical care pathways**

The need for clear pathways for accessing psychiatric services for patients with emergent psychiatric side effects suspected to be related to isotretinoin has been highlighted. Clinical practice across the UK varies and some centres have formal or informal pathways in place, however these services are very variable.

Patients and their families have highlighted a need for clear pathways for accessing support and care for side effects as the majority of side effects are unrelated to dermatology. In particular, the need for referrals to investigate and treat sexual side effects.

## **6.12. Research**

The need for further research to gain greater insight into the risks of psychiatric and sexual side effects and how these may be minimised, managed or treated has been acknowledged. However, it is also important to consider the difficulties associated with designing and completing a suitable study to address the outstanding concerns.

High-quality studies to definitively address the ongoing concerns associated with isotretinoin would require very large numbers of patients, in multiple centres over a long period, due to the high community prevalence of mental health disorders and the low numbers of suspected cases due to isotretinoin. A registry may be required in order to prospectively collect this type of data.

Possible areas for further research include:

- Investigating dosing regimens
- Identifying potential risk factors for side effects
- Clarifying the nature and extent of the risks both during and after treatment cessation
- Determining risks in individuals with pre-existing and/or family history of mental health conditions
- Establishing a causal association with psychiatric and sexual side effects
- Monitoring compliance with the terms of the licence
- Evaluating the effectiveness of risk minimisation measures

## 7. REGULATORY OPTIONS

This chapter provides an overview of the regulatory options considered by the Isotretinoin EWG.

### 7.1. Consideration of regulatory options

The Isotretinoin EWG and subsequently the CHM, considered a range of regulatory options in relation isotretinoin. These included:

a) To remove isotretinoin from the UK market

This is an option when the risks of a medicine outweigh its potential benefits in all patients.

b) To further restrict how isotretinoin can be used in the UK

This is an option when there is strong evidence that the risks of a medicine outweigh the benefits for a defined group of patients.

Options to restrict the use of a medicine included:

- Introducing a contraindication in a particular patient population

This option would be appropriate if a patient population could be identified where the risks of the medicine outweigh the benefits.

- restriction of the dose

This option would be appropriate if there was evidence that the risks of the medicine were dose dependent and a dose could be identified which reduced the risk of a side effect while retaining acceptable efficacy.

- Introducing restrictions around who could prescribe a medicine

This option could be appropriate if additional expertise was required in order to safely prescribe the medicine or monitor the patient during treatment.

c) Require changes to the educational materials produced to support safe use of isotretinoin

This option would be appropriate if additional interventions are required to prevent or reduce the occurrence of side effects or to reduce their severity or impact on the patient should side effects occur. Educational materials are produced by the MAH following approval by the MHRA. They are used to help patients and healthcare professionals understand and reduce certain risks. They may include brochures and forms.

d) Require changes the product information for isotretinoin

This option would be appropriate if new data were available on the magnitude and/or nature of the risk of psychiatric and sexual side effects such that the current warnings in the SmPC and PIL did not fully reflect the available evidence.

e) To take no further action

This option would be appropriate if the current regulatory position fully reflected all the available evidence and the current measures were considered adequate to manage the risks.

## 7.2. CHM discussion

The CHM considered the evaluation of the Isotretinoin EWG and advised that, given the evidence from stakeholders and the data considered during the review, the overall balance of risks and benefits for isotretinoin remained favourable, however further action should be taken to ensure patients are fully informed about isotretinoin and are effectively monitored during and after treatment. Therefore the option to take no action was not supported.

The CHM considered the option of removal of isotretinoin from the UK market, taking into account the compelling evidence from stakeholders on both the impact of the side effects of isotretinoin and of the benefits of treatment and the totality of the available evidence. The CHM advised that the balance of risks and benefits of isotretinoin in the treatment severe forms of acne resistant to adequate courses of standard therapy with systemic antibacterials and topical therapy remains favourable, but further action should be taken to ensure patients are fully informed about potential risks of treatment and are effectively monitored during and after treatment. Therefore, the option to remove isotretinoin from the market was not supported.

The CHM noted the current restrictions to the use of isotretinoin in the UK and discussed whether the evidence supported further restrictions. In particular, the concerns of stakeholders regarding the risk of side effects in adolescents and proposals for restricting use of isotretinoin in this age group were carefully considered. However, it was concluded that there was not sufficient evidence to support an increased risk of side effects in adolescents under the age of 18 years compared to other age groups treated with isotretinoin.

Delaying treatment for severe acne could be associated with long term scarring which may be associated with significant psychological harm. After considering the available information, it was concluded that the current evidence did not support a contraindication in adolescents under 18 years but it was agreed that more must be done to ensure appropriate prescribing for young patients.

Although specific increased risks were not identified within the under 18 age group treated with isotretinoin, compared with older age groups, significant concerns were raised by stakeholders that had both positive and negative views about isotretinoin, regarding the provision of information and inconsistencies in monitoring of patients. It was recommended that until further data on the level of risk could be established in this age group, there should be greater oversight of these patients and their treatment. It was recommended that to support greater oversight of these patients, two specialist prescribers must agree that isotretinoin is an appropriate treatment and explain the risks as well as the benefits of treatment.

It was recommended that the need for further evidence on the risks for adolescents should be addressed within the call for further research and the wider communications.

It was noted that a number of clinical issues had been raised during the review and that any recommendations considered outside the regulatory remit of the MHRA should be taken forward with the relevant organisations.

The role of specialists in managing patients treated with oral isotretinoin was discussed. It was noted that in the UK this has meant treatment by or under the supervision of a consultant dermatologist, but that the role of GP with extended roles in dermatology (GPwERs) could potentially be further explored. The importance of communicating the recommendations of the review with prescribers was emphasised and the need for clear guidance reinforced.

The concerns of stakeholders regarding the need to provide information tailored to the different age groups, potentially using different modes of communication as well as the need for clarity on the different names under which isotretinoin is marketed was discussed. It was acknowledged that



information needs to be provided to patients before the medicine is prescribed or dispensed. It was noted that awareness is key to minimising the risk of tragic events and that patients need to know what might happen and how to get help. The importance of ensuring that the new measures are practical and do not become a barrier to treatment for those with severe acne who may require treatment with isotretinoin was discussed and it was acknowledged that stakeholder input would be essential in the development of materials.

It was agreed that the SmPC, the PIL, and the educational materials produced by the MAHs should all be updated with input from stakeholders.

## 8. RECOMMENDATIONS OF THE CHM

The CHM considered the evaluation and recommendations of the Isotretinoin EWG and issued the following recommendations.

### 8.1. Consideration of the balance of risks and benefits of isotretinoin

Stakeholders expressed strong views on benefit-risk balance, with some describing it positively as a life-changing medicine and others wanting it taken off the market or severely restricted due to concerns about severe adverse effects, including suicide and the risk of effects persisting after the end of treatment.

The CHM considered the available information on the risk of psychiatric and sexual side effects.

The CHM considered the limitations in the data from the Yellow Card Scheme and scientific literature which are insufficient to establish causal associations for many of the acute and longer term psychiatric and sexual side effects reported with the use of isotretinoin. However uncertain at present, an association cannot be ruled out and the individual experiences of patients continue to raise concern, highlighting the need to raise awareness of the risks. The CHM also acknowledged that for some patients with severe acne that had failed to respond to antibiotics or topical treatments, including acne at risk of scarring, isotretinoin was the only effective treatment available, and many stakeholders had reported that it had been hugely beneficial to them.

The CHM agreed that for patients with severe acne resistant to antibiotics and topical treatments the overall balance of risks and benefits remains favourable, but further action should be taken to ensure patients are fully informed about isotretinoin and are effectively monitored during and after treatment.

The CHM agreed that there was insufficient information to support a contraindication in any patient group.

### 8.2. Consideration of regulatory action

#### 8.2.1. Changes to product information

Stakeholders raised concerns that information on the nature and frequency of side effects in the product information for isotretinoin was misleading and that the Yellow Card data underestimated the frequency of side effects due to underreporting.

There was particular concern about the lack of information on sexual side effects and of the long-term nature of some side effects.

The Isotretinoin EWG and the CHM considered the warnings in the current product information and whether these accurately reflected the risks relating to psychiatric and sexual disorders.

In relation to psychiatric side effects, the current warnings are considered to reflect the available data and aligned with the experiences of patients, documented in case reports and testimonies received during the review. However, it was noted from many of the testimonies, that patients and their families were not made aware of the warnings prior to treatment with isotretinoin.

The CHM considered the frequency of listed psychiatric side effects within the regulatory framework and noted the concerns of stakeholders about the accuracy of these. They concluded that it was not possible to define more accurate frequencies at this time due to a number of factors, including: confounding by indication and patient population; limitations in the clinical development programme; limited availability of age specific usage data; and methodological differences in the available literature studies. However, the CHM noted that the frequency estimates for some psychiatric side effects in the product information are considerably lower than the background incidence of such events in the general population which may result in confusion or misinterpretation of the level of risk. Therefore it is proposed that the frequency in the product information is changed to 'not known' which is the frequency category used to reflect safety concerns where it is not possible to provide an accurate estimate of the frequency. This frequency category is routinely used for safety concerns identified from spontaneous case reports and pharmacovigilance monitoring.

However, further information about these risks, their uncertainties and the background rates should be provided to patients noting that the presentation of this information should be carefully explored with stakeholders prior to implementation. It will be important to ensure the message that the level of risk could be greater than previously suggested and could be higher in younger age groups is conveyed to patients in an age-appropriate way and their parents or carers are also informed.

The product information currently includes a statement warning that psychiatric side effects may persist after stopping treatment and it was recommended that there should be a similar warning about the possible occurrence of sexual side effects and that these may continue long term after stopping treatment with isotretinoin. It was recommended that the current list of side effects in SmPC of sexual dysfunction including erectile dysfunction, decreased libido, gynaecomastia and vulvovaginal dryness should be expanded to include the additional side effects: orgasm difficulties and genital hypoaesthesia.

The product information currently includes a general statement that some side effects may persist after treatment has stopped. The CHM considered information about some patients experiencing long term side effects other than psychiatric or sexual side effects. However, a lack of sufficient information available on these effects meant that it was not possible to define the risk for symptoms continuing long term or identify specific risk factors to support amending the existing warning. Further research is needed to establish the extent of the risk of side effects continuing long term and this is considered under section 8.5 below.

***It is recommended that:***

Given the concerns about the lack of robust evidence to support the accuracy of current frequency estimates for psychiatric side effects in the product information, current information on the frequency of psychiatric side effects (depression, depression aggravated, suicide, suicidal attempt and suicidal ideation) in the Summary of Product Characteristics (SmPC) and Patient Information Leaflet (PIL) should be changed to 'not known'. Careful consideration must be given to how these risks are explained to patients and supported by educational materials.

Warnings about the potential for the sexual side effects (erectile dysfunction, vulvovaginal dryness, reduced libido, orgasm difficulties and genital hypoaesthesia) to continue long-term after treatment with isotretinoin has been stopped should be added to the SmPC and PIL.

Although the data are limited, it is considered that there is sufficient evidence to justify adding orgasm difficulties and genital hypoaesthesia as possible side effects in the SmPC and PIL.

### 8.2.2. Counselling, information provision and monitoring

Patients and their families called for clear information about side effects to be shared with patients before they started treatment with isotretinoin and for regular monitoring of patients during treatment. It is clear from the information provided by stakeholders that the patient experience varies between clinics and that there is a desire for a more consistent approach so that patients and their families know what to expect and can make informed decisions.

Some stakeholders reported a lack of acceptance among clinicians that isotretinoin might be causing the side effects they were experiencing and described a lack of support for people experiencing side effects, with no clear pathways for accessing support as the majority of side effects are unrelated to dermatology.

A number of stakeholders called for a cooling off period between the patient being counselled about the side effects of isotretinoin and a decision being made about initiating treatment and the first prescription issued.

The CHM emphasised that isotretinoin is authorised for treatment of severe acne that has failed to respond to antibiotics and topical treatments, and that it should not be prescribed as first line or in moderate or mild disease. The CHM discussed the complexity of the relationship between acne and possible psychiatric and sexual side effects and the importance of the awareness to ensure patients seek and receive appropriate support. It was noted that there was considerable variation in counselling and monitoring of patients in clinical practice across the UK.

#### ***It is recommended that for:***

##### *Psychiatric side effects*

- The SmPC and PIL should be updated to state that patients, and where applicable parents or carers, must be counselled about the risk of possible psychiatric side effects with isotretinoin prior to prescription of isotretinoin, and ideally prior to any referral that might include consideration of isotretinoin treatment.
- The SmPC and PIL should be updated to state that patient's mental health status should be assessed prior to prescription of isotretinoin and regularly during treatment for developing or worsening psychiatric disorders.
- To support consistent implementation of the regulatory change further work involving professional bodies and health system organisations will be required to determine appropriate tools (e.g. questionnaires) to assess mental health status; periodicity of monitoring and clinical pathways to manage patients with severe or ongoing psychiatric disorders during or after treatment with isotretinoin.

##### *Sexual disorders*

- The SmPC and PIL should be updated to state that patients, and where applicable parents or carers, must be counselled about the possible risk of sexual dysfunction with isotretinoin prior to the prescribing decision, and ideally prior to any referral that might include consideration of isotretinoin treatment. The age and maturity of the patient should be taken into account in considering the most appropriate counselling approach, including giving the option to discuss without parents or carers present.

- To support consistent implementation of the regulatory change further work involving professional bodies and health system organisations will be required to determine appropriate tools (e.g. age-appropriate questionnaires) to assess sexual function; periodicity of monitoring and clinical pathways to manage patients with sexual dysfunction during or after treatment with isotretinoin.

#### *Information for patients*

- Information in a range of formats should be developed to provide accessible, plain language information to patients under consideration for isotretinoin treatment, and where appropriate their parents or carers, taking account of the recommendations on psychiatric and sexual side effects above. This information should include:
  - reference to the possibility of side effects continuing after treatment has stopped.
  - information on the self-management of common side effects such as skin dryness.
  - a process for facilitating discussion, understanding and acknowledgement of the possible risks of treatment.
- Patients and their parents/carers should have adequate time between initial counselling and subsequent prescription to reflect on the information about isotretinoin and ask questions before prescription of isotretinoin.

#### *Acknowledgement of risk form*

Patients and parents/carers should receive full information about the possible risks as well as the benefits of treatment in order to be able to make an informed decision about their treatment. There is currently an acknowledgement of risk form for female patients. It was recommended that this form is expanded to cover all potential risks and used for all patients. Stakeholders, including patients, parents/carers and healthcare professionals, should be involved in the development of the form to ensure it meets requirements.

### **8.3. Consideration of restriction of isotretinoin use in adolescents**

Some stakeholders raised concerns about whether isotretinoin was suitable for younger patients whose stage of development might put them at increased risk of side-effects, and who may not fully understand the risks they may be taking. Some called for the use of isotretinoin to be restricted in those under the age of 18 years.

Some stakeholders also felt that isotretinoin was prescribed inappropriately, to those who did not have severe acne.

Currently isotretinoin should not be used for the treatment of prepubertal acne and is not recommended in adolescents less than 12 years of age due to a lack of data on efficacy and safety. The concerns of stakeholders regarding the risk of side effects in adolescents and proposals for restricting use of isotretinoin in this age group were considered carefully. However, it was advised that there was not sufficient evidence to support the suggestion that adolescents under the age of 18 years are at an increased risk of experiencing side effects compared to other age groups receiving isotretinoin.

Delaying treatment for severe acne could be associated with long term scarring which may be associated with significant psychological harm. Therefore the current evidence did not support a

contraindication in adolescents under 18 years but it was agreed that more must be done to ensure appropriate prescribing for young patients.

Although specific increased risks were not identified within the under 18 age group treated with isotretinoin, compared with older age groups, significant concerns were raised by stakeholders that had both positive and negative views about isotretinoin, regarding the provision of information and inconsistencies in monitoring of these patients. It was recommended that until further data on the level of risk could be established in this age group there should be greater oversight of these patients and their treatment with two healthcare professionals agreeing it is appropriate before treatment is prescribed and initiated within the consultant dermatologist led team. The agreement by the two healthcare professionals should be documented within the risk minimisation materials.

It was recommended that there is a need for further evidence on the risks for adolescents and this should be addressed within the call for further research and the wider communications.

***It was recommended that:***

More data are needed on the use of isotretinoin in adolescents under 18 years of age, including any long-term effects in adulthood and recommended longitudinal studies would be of benefit.

Adolescents under 18 years of age should be treated by a healthcare professionals with appropriate expertise in treating children and young people, ideally in a setting that is able to support the appropriate counselling of patients and parents or carers for the above risks and with an identified appropriate care pathway if side effects occur.

There should be greater oversight of isotretinoin treatment in those under 18 years, including agreement by two healthcare professionals that isotretinoin is the most appropriate treatment option before it is prescribed and that patients and their families have been adequately informed about the potential risks.

#### **8.4. Consideration of the roles and responsibilities of healthcare professionals**

Prescription of isotretinoin is currently permitted only under the supervision of consultant dermatologists. Some healthcare professional stakeholders questioned whether GPs with specialist training and expertise in dermatology should also be able to prescribe isotretinoin.

It was noted that the SmPC states that isotretinoin should only be prescribed by or under the supervision of physicians with expertise in the use of systemic retinoids for the treatment of severe acne and a full understanding of the risks of isotretinoin therapy and monitoring requirements. In the UK this has been interpreted such that isotretinoin is restricted to consultant dermatologists or other healthcare professionals with appropriate expertise working as part of a consultant-led team.

The role of general practitioners with an extended role in dermatology (GPwERs) in the management of acne in adults was discussed. It was noted that GPs are experienced in managing mental health and sexual health issues, and that GPwERs have additional training in dermatology, with some currently prescribing isotretinoin as part of consultant-led teams.<sup>44 45</sup>

<sup>44</sup> There may be GPwERs who are prescribing isotretinoin independently, integrated with secondary care with care pathways agreed by local dermatology consultants.

<sup>45</sup> Guidance from the RCGP state that prescribing of isotretinoin by a GPwER is an 'off-licence' indication as in the UK the physicians with expertise in the use of systemic retinoids refers to consultant dermatologists. (Guidance and competences to support the accreditation of GPs with Extended Roles (GPwERs) in Dermatology (including Skin Surgery), Royal College of General Practitioners, 2019)

***It was recommended that:***

The potential for GPwERs to independently prescribe isotretinoin for adult patients should be explored with the appropriate professional bodies and reflected in clinical guidance. There should be clear communication from dermatology services to general practice that a patient has started treatment with isotretinoin. Emphasis is placed on clear communications notifying all involved healthcare professionals of any problems experienced by the patient.

**8.5. Consideration of further research**

Stakeholders called for more research on the side effects of isotretinoin and how they could be treated. For example, whether particular side-effects can continue long-term, whether some patients are at more risk than others, and how such effects are best managed.

The main limitation of the data is that it is insufficient to establish causal associations with either psychiatric or sexual side effects and the use of isotretinoin. However, an association cannot be ruled out and the individual experiences of patients continue to raise concerns.

The need for further research to gain greater insight into the risks of psychiatric and sexual side effects and how these may be minimised, managed or treated has been acknowledged. However, it is also important to consider the difficulties associated with designing and completing a suitable study to address the outstanding concerns. For example, the very high background incidence of poor mental health in patients with severe acne would mean that any controlled clinical trial designed to establish a causal relationship between isotretinoin and psychiatric disorders would have to be impractically large and would require recruitment of a control group whose severe acne would go untreated, which presents ethical challenges. The CHM recommended that a drug registry should be developed to collect patient level data and that the governance and funding for the registry should be determined through consultation with stakeholders.

The CHM also welcomed the call for research published by the National Institute for Health Research on 22 July 2021 on 'Benefits and harms of maintenance therapy for refractory acne vulgaris or previous relapses by reduced dose isotretinoin regimens'.

***It was recommended that:***

More research is needed on the side effects associated with isotretinoin, including their frequency, the biological mechanisms underlying their occurrence, the identification of any relevant biomarkers and genetic factors.

More data are needed on the use of isotretinoin in adolescents under 18 years of age, including the study of any potential long-term effects in adulthood and suggested longitudinal studies would be of benefit.

An isotretinoin drug registry should be developed to:

- gather further information on psychiatric events and sexual dysfunction with isotretinoin including the nature and magnitude of risks associated with isotretinoin, risk factors, natural progression of events, vulnerable age groups and the complex relationship between psychiatric events and sexual disorders.
- Facilitate identification of adverse events which are currently not listed in the product information, the frequency of side effects and gather information and understanding on side

effects which continue long term as well as the onset of adverse events after isotretinoin treatment has stopped.

Applied research should be conducted to evaluate the impact of the new risk minimisation measures.



## REFERENCES

- Abali, R., Yuksel, M. A., Aktas, C., Celik, C., Guzel, S., Erfan, G., & Sahin, O. (2013). Decreased ovarian reserve in female Sprague–Dawley rats induced by isotretinoin (retinoic acid) exposure. *Reprod Biomed Online*, 184-191.
- Abdelmaksoud, A., Lotti, T., Anadolu, R., Goldust, M., Ayhan, E., Dave, D. D., . . . Gupta, M. (2020). Low dose of isotretinoin: A comprehensive review. *Dermatol Ther.*, e13251.
- Acmaç, G., Cinar, L., Acmaç, B., Aksoy, H., Kafadar, Y. T., Madendag, Y., . . . Muderris, I. (2019). The Effects of Oral Isotretinoin in Women with Acne and Polycystic Ovary Syndrome. *Biomed Res Int.*, Article ID 2513067.
- Adama, J. (2010). The neurobehavioural teratology of retinoids: a 50-year history. *Birth Defects Res A Clin Mol Teratol*, 895-905.
- Addington, J., & Heinsen, R. (2011). Prediction and prevention of psychosis in youth at clinical high risk. *Annu Rev Clin Psychol*.
- Addington, J., Coldham, E. L., Jones, B., Ko, T., & Addington, D. (2003). The first episode of psychosis: the experience of relatives. *Acta Psychiatr Scand*, 285-289.
- Agarwal, U. S., Besarwal, R. K., & Bhola, K. (2011). Oral isotretinoin in different dose regimens for acne vulgaris: a randomized comparative trial. *Indian J Dermatol Venereol Leprol*, 688-94.
- Akman, A., Durusoy, C., Senturk, M., Koc, C. K., Soyuturk, D., & Alpsoy, E. (2007). Treatment of acne with intermittent and conventional isotretinoin: a randomized, controlled multicenter study. *Arch Dermatol Res*, 467-73.
- Aksoy, H., Cinar, L., Acmaç, G., Aksoy, U., Aydin, T., Vurdem, U. E., . . . Kartal, D. (2015). The effect of isotretinoin on ovarian reserve based on hormonal parameters, ovarian volume, and antral follicle count in women with acne. *Gynecol Obstet Invest*, 78-82.
- Akturk, A. S., Abali, R., Yuksel, M. A., Guzel, E. C., & Kiran, R. (2014). The effects of isotretinoin on the ovarian reserve of females with acne. *Gynecol Endocrinol*, 30-33.
- Al Alawi, M., Al Sinawi, H., Al Qasabi, A. M., Al Mamari, A. M., Panchatcharam, S. M., & Al-Adawi, S. (2018). Prevalence and predictors of depressive symptoms among attendees of a tertiary care dermatology clinic in Muscat, Oman. *International Journal of Dermatology*, 284-290.
- Al Ghofaili, F. A. (2021). Isotretinoin Use and Risk of Depression in Acne Vulgaris Patients in Riyadh, Saudi Arabia. *Cureus*, e13680.
- Algamdi, B. N., Aldahlan, H. W., AlAlhareth, H., Alghamdi, R., Alkhouzaie, M. T., ALahmari, N., . . . ALghamdi, K. (2020). Evaluating Depression Among Acne Vulgaris Patients Treated With Isotretinoin. *Cureus*, e12126.
- Almeida, O. P., Flicker, L., Lautenslager, N. T., Leedman, P., Vasikaran, S., & van Bockxmeer, F. M. (2005). Contribution of the MTHFR gene to the causal pathway for depression, anxiety and cognitive impairment in later life. *Neurobiol Aging*, 251-257.
- Al-Radideh, O., Chan, K. H., Gupta, S., Slim, J., & Bellary, S. (2021). Concurrent Serotonin Syndrome and Prolong QT Interval Induced by Paroxetine Overdose With Isotretinoin. *Cureus*, e14497.

- Alzoubi, K. H., Khabour, O. F., Hassan, R. E., Qarqaz, F., Al-Azzam, S., & Mhaidat, N. (2013). *Int J Clin Pharmacol Ther*, 631-40.
- Amory, J. K., Ostrowski, K. A., Gannon, J. R., Berkseth, K., Stevison, F., Isoherranen, N., . . . Walsh, T. (2017). Isotretinoin administration improves sperm production in men with infertility from oligoasthenozoospermia: a pilot study. *Andrology*, 1115-1123.
- Apple, D. M., Fonesca, R. S., & Kokovay, E. (2016). The role of adult neurogenesis in psychiatric and cognitive disorders. *Brain Res*, Epub.
- Arlington, V. A. (2013). Diagnostic and statistical manual of mental disorders (5th ed.). . *American Psychiatric Association.*, <https://doi.org/10.1176/appi.books.9780890425596.dsm05>.
- Asai, Y., Baibergenova, A., Dutil, M., Humphrey, S., Hull, P., Lynde, C., . . . Zip, C. (2016). Management of acne: Canadian clinical practice guideline. *CMAJ*, 118-126.
- Bagatin, E., Costa, C. S., Rocha, M., Picosse, F. R., Kamamoto, C., Pirmez, R., . . . Miot, H. (2020). Consensus on the use of oral isotretinoin in dermatology - Brazilian Society of Dermatology. *Anais Brasileiros de Dermatologia*, 19-38.
- Barnes, L. E., Levender, M. M., Fleischer Jr, A. B., & Feldman, S. R. (2012). Quality of Life measures for acne patients. *Dermatology Clinical*, 293-300.
- Baugh, C. M., Malone, J. H., & Butterworth, C. E. (1968). Human biotin deficiency: A case history of biotin deficiency induced by raw egg consumption in a cirrhotic patient. . *Am J Clin Nutr*, 173.
- Blasiak, R. C., Stamey, C. R., Burkhart, C. N., Lugo-Somolinos, A., & Morell, D. S. (2013). High-dose isotretinoin treatment and the rate of retreat, relapse, and adverse effects in patients with acne vulgaris. *JAMA Dermatol*, 1392-8.
- Borovaya, A. O. (2013). Review: Does isotretinoin therapy of acne cure or cause depression? *International Journal of Dermatology*, 1040-1052.
- Botsali, A., Kocyigit, P., & Uran, P. (2020). The effects of isotretinoin on affective and cognitive functions are disparate in adolescent acne vulgaris patients. *Journal of Dermatological Treatment*, 734-738.
- Boudou, P., Chivot, M., Vexiau, P., Villette, J. M., Julien, R., Belanger, A., & Fiet, J. (1994). Evidence for decreased androgen 5 alpha-reduction in skin and liver of men with severe acne after 13-cis-retinoic acid treatment. *J Clin Endocrinol Metab*, 1064-9.
- Boudou, P., Soliman, H., Chivot, M., Vilette, J. M., Vexiau, P., Belanger, A., & Fiet, J. (1995). Effect of oral isotretinoin treatment on skin androgen receptor levels in male acneic patients. *J Clin Endocrinol Metab*, 1158-61.
- Bray, A. P., Kravvas, G., Skevington, S. M., & Lovell, C. R. (2019). Is there an association between isotretinoin therapy and adverse mood changes? A prospective study in a cohort of acne patients. *Journal of Dermatological Treatment*, 796-801.
- Bremner, J. D. (2005). Functional brain imaging alterations in acne patients treated with isotretinoin. *Am J Psychiatry*, 983-91.
- Bremner, J. D. (2012). Retinoic acid and affective disorders: The evidence for an association. *J Clin Psych*, 37-50.

- Bremner, J. D., Fani, N., Ashraf, A., Votaw, J. R., Brummer, M. E., Cummins, T., . . . Nemeroff, C. B. (2005). Functional brain imaging alterations in acne patients treated with isotretinoin. *Am J Psychiatry*, 983-991.
- Bressa, G. M. (1994). S-adenosyl-l-methionine (SAME) as antidepressant: meta-analysis of clinical studies. . *Acta Neurol Scand*, 7-14.
- Campos-Munoz, L., Lopez-De Lara, D., Conde-Taboada, A., Fueyo Casado, A., & Lopez-Bran, E. (2020). Depression in transgender adolescents under treatment with isotretinoin. *Journal of Experimental Dermatology*, 615-616.
- Charles, B. M., Hosking, G., Green, A., Pollitt, R., Bartlett, K., & Taitz, L. S. (1979). Biotin-responsive alopecia and developmental regression. *Lancet*, 118-120.
- Charles, B. M., Hosking, G., Green, A., Pollitt, R., Bartlett, K., & Taitz, L. S. (1979). Biotin-responsive alopecia and developmental regression. *Lancet*, 118.
- Cinar, L., Kartal, D., Ergin, C., Aksoy, H., Karadag, M., Aydin, T., . . . Borlu, M. (2016). The effect of systemic isotretinoin on male fertility. *Cutan Ocul Toxicol.*, 296-299.
- Cinar, S. L., Kartal, D., Aksoy, H., Cinar, E., Aydin, T., Oz, L., . . . Borlu, M. (2017). Long-term effect of systemic isotretinoin on female fertility. *Cutan Ocul Toxicol*, 132-134.
- Coleman, R., & MacDonald, D. (1994). Effects of isotretinoin on male reproductive system. *Lancet*, 198.
- Comitato, R., Esposito, T., Cerbo, G., Angelini, F., & Varriale, B. (2006). Apoptosis explains isotretinoin's action and adverse effects. Impairment of spermatogenesis and enhancement of testicular germ cell apoptosis induced by exogenous all-trans-retinoic acid in adult lizard *Podarcis sicula*. *J Exp Zool A Comp Exp Bio*, 288-298.
- Cordain, L., Lindeberg, S., Hurtado, M., Hill, K., Eaton, S. B., & Brand-Miller, J. (2002). Acne vulgaris: a disease of Western civilization. *Arch Dermatol*, 1584-90.
- Cotterill, J. A., & Cunliffe, W. J. (1997). Suicide in dermatological patients. *British Journal of Dermatology*, 246-250.
- Crandall, J. E., Sakai, Y., Zhang, J., Koul, O., Mineur, Y., & Crusio, W. E. (2004). . 13-cis retinoic acid suppresses hippocampal cell division and hippocampal dependent learning in mice. . *Proc Nat Acad Sci USA*, 5111-5116.
- Crossland, H., Constantin-Teodosiu, D., Gardiner, S. M., Constantin, D., & Greenhaff, P. L. (2008). A potential role for Akt/ FOXO signalling in both protein loss and the impairment of muscle carbohydrate oxidation during sepsis in rodent skeletal muscle. *J Physiol*, 5589-600.
- Crow, S. J., & Eckert, E. D. (2016). Anorexia nervosa and bulimia nervosa. *The Medical Basis of Psychiatry*, 4th Ed, 211-228.
- Csoka, A., & Szyf, M. (2009). Epigenetic side effects of common pharmaceuticals. *Med Hypotheses*, 770-80.
- Cunningham, L. (2020). Mucocutaneous adverse effects of the genital and perianal skin from isotretinoin therapy. *J Am Acad Dermatol.*, 1174-1175.

- Daunton, A., Oyeboode, F., & Goulding, J. M. (2019). Depression and the dermatologist: a critical analysis of contemporary isotretinoin prescribing practices. *Clin Exp Dermatol*, 903-5.
- Dawson, A. L. (2013). Acne vulgaris. *BMJ*, f2634.
- De Almeida Seigneur D'albuquerque, M., Sokoloski, V., Loureiro, M., Martello Panno, S., & Mazzillo, M. (2020). Pityriasis rubra pilaris: a rare chronic disease. *Journal of Dermatology Nurses' Association*.
- Dellavalle, R. (2017). BMJ Best Practice - Acne Vulgaris. *BMJ*.
- Dellavalle, R., & Howland, A. (2017). Acne vulgaris. *BMJ*.
- Dessinioti, C., Zouboulis, C. C., Bettoli, V., & Rigopoulos, D. (2020). Comparison of guidelines and consensus articles on the management of patients with acne with oral isotretinoin. *J Eur Acad Dermatol Venereol*, 2229-2240.
- Dhaked, D. R., Meena, R. S., Maheshwari, A., Agarwal, U. S., & Purohit, S. (2016). A randomized comparative trial of two low-dose oral isotretinoin regimens in moderate to severe acne vulgaris. *Indian Dermatol Online*, 378-385.
- Ding, J., Kam, W. R., Dieckow, J., & Sullivan, D. A. (2013). The Influence of 13-cis Retinoic Acid on Human Meibomian Gland Epithelial Cells. *Invest Ophthalmol Vis Sci*, 4341-4350.
- Droitcourt, C., Poizeau, F., Kerbrat, S., Balusson, F., Drezen, E., Happe, A., . . . Dupuy, A. (2019). Isotretinoin and risk factors for suicide attempt: a population-based comprehensive case series and nested case–control study using 2010–2014 French Health Insurance Data. *Journal of the European Academy of Dermatology and Venereology*, 1293-1301.
- Duman, R. S. (2004). Depression: a case of neuronal life and death? *Biol Psychiatry*, 140-145.
- Dunn, L. K., O'Neill, J. L., & Feldman, S. R. (2011). Acne in adolescents: quality of life, self-esteem, mood, and psychological disorders. *Dermatol Online J*.
- Elhusein, B., Elkhaled, W., Koodoruth, M. A., Kumar, R., & Al Abdulla, M. (2020). Isotretinoin-induced psychotic episode in a 17-year-old adolescent male. *SAGE Open Med Case Rep*.
- Erdogan, Y., Erturan, I., Aktepe, E., & Akyildiz, 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. *Paediatric Drugs*, 195-202.
- Faghihi, G., Mokhtari, F., Fard, N. M., Motamedi, N., & Hosseini, S. M. (2017). Comparing the Efficacy of Low Dose and Conventional Dose of Oral Isotretinoin in Treatment of Moderate and Severe Acne Vulgaris. *J Res Pract*, 233-238.
- Fakour, Y., Noormohammadpour, M. D., Ameri, H., Ehsani, A. H., Mokhtan, L., Khosrovanmehr, N., & Hoseini neshad, S. Z. (2014). The Effect of Isotretinoin (Roaccutane) Therapy on Depression and Quality of Life of Patients with Severe Acne. *Iran J Psychiatry*, 237-240.
- Feily, A., Taheri, T., Meier-Schisser, B., Rhinehart, D. P., Sobhanian, s., Colon-Diaz, M., . . . Ramirez-Fort, M. K. (2019). The effect of low-dose isotretinoin therapy on serum androgen levels in women with acne vulgaris. *Int J Womens Dermatol*, 102-104.
- Fenton, C., & Kang, C. (2021). Isotretinoin is key in treating acne vulgaris. *Drugs and Therapy Perspectives*, 150-156.

- Fornaro, M. (2010). Obsessive-compulsive disorder with bipolar diathesis following isotretinoin therapy remitting upon treatment with olanzapine and fluvoxamine. *Neuropsychiatr Dis Treat*, 719-22.
- Ghods, S. Z., Orawa, H., & Zouboulis, C. C. (2009). Prevalence, severity, and severity risk factors of acne in high school pupils: a community-based study. *J Invest Dermatol*.
- Goodfield, M. J., Cox, N. H., Bowser, A., McMillan, J. C., Millard, L. G., Simpson, N. B., & Ormerod, A. D. (2010). Advice on the safe introduction and continued use of isotretinoin in acne in the U.K. 2010. *Br J Dermatol*, 1172-9.
- Gorton, H. W. (2016). Non-psychotropic medication and risk of suicide or attempted suicide: a systematic review. . *British Medical Journal*, 6:e009074.
- Griffin, J. N., Pinali, D., Olds, K., Lu, N., Appleby, L., & Doan, L. (2010). 13-cis-Retinoic acid decreases hypothalamic cell number in vitro. *Neurosci Res*, 185-190.
- Gupta , N., & O'Shea, T. (2020). Oral isotretinoin prescribing in primary care: A landmark service audit. *100th Annual Meeting of the British Association of Dermatologists*, 76-77.
- Haebich, G., & El-Dars, L. (2020). Real-world data on medical management of hidradenitis suppurativa: A national audit. . *British Journal of Dermatology*, 37-38.
- Halkier-Sorensen, L. (1988). Sexual dysfunction in a patient treated with etretinate. *Acta Derm Venereol.*, 90-91.
- Hanna, K. A. (2016). Affective disorders as potential complication of anti-acne treatment with isotretinoin: A case series. *J Affect Disord*, 154-158.
- Hasan, S., & Ingram, J. (2020). Current management of hidradenitis suppurative in the UK. *British Journal of Dermatology*, 51-52.
- Haybaeck, J., Postruznik, M., Miller, C. L., Dulay, J. R., Llenos, I. C., & Weis, S. (2015). Increased expression of retinoic acid-induced gene 1 in the dorsolateral prefrontal cortex in schizophrenia, bipolar disorder, and major depression. *Neuropsychiatr Dis Treat*, 279-289.
- Healy, D., Le Noury, J., & Mangin, D. (2018). Enduring sexual dysfunction after treatment with antidepressants, 5 alpha reductase inhibitors and isotretinoin: 300 cases. *International Journal of Risk and Safety in Medicine*, 29, 125-134.
- Hekmatjah, J., Chat, V. S., Sierro, T., Read, C., Kassardjian, A., & Armstrong, A. W. (2020). 371 Acne patients on isotretinoin experience less psychological distress and depression symptoms compared to those on oral antibiotics. *Journal of Investigative Dermatology*.
- Hogan , C., Le Noury, J., Healy, D., & Mangin, D. (2014). One hundred and twenty cases of enduring sexual dysfunction following treatment. *The International Journal of Risk and Safety in Medicine*, 109-116.
- Hu, P., Wang, Y., Liu, J., Meng, F. T., Qi, X. R., & Chen, L. (2016). Chronic retinoic acid treatment suppresses adult hippocampal neurogenesis, in close correlation with depressive-like behaviour. *Hippocampus*, 911-923.
- Huang, Y. C., & Cheng, Y. C. (2017). Isotretinoin treatment for acne and risk of depression: A systematic review and meta-analysis. *J Am Acad Dermatol*.

- Imam, M. S., Abdel-Sattar, R. M., Aldajani, G. A., Alsultan, R. S., & Aldajani, Y. A. (2021). Knowledge And Awareness Of Acne Patients About Isotretinoin Use And Safety In Dawadmi Governorate, Riyadh Region, Saudi Arabia. *Systematic Reviews in Pharmacy*, 71-75.
- Jensen, K. V., & Abba-Aji, A. (2020). Isotretinoin-Induced Delusional Disorder, Somatic Subtype. *Case Rep Dermatol Med*.
- Kamm, J. J. (1982). Toxicology, carcinogenicity, and teratogenicity of some orally administered retinoids. *J Am Acad Dermatol*, 652-659.
- Karadag, A. S., Ertugrul, D. T., Tural, E., & Akin, K. O. (2010). Short term isotretinoin treatment decreases insulin-like growth factor-1 and insulin-like growth factor binding protein-3 levels: does isotretinoin affect growth hormone physiology? *Br J Dermatol.*, 798-802.
- Karadag, A. S., Ertugrul, D. T., Tural, E., & Akin, K. O. (2011). Isotretinoin influences pituitary hormone levels in acne patients. *Acta Derm Venereol.*, 31-34.
- Karadag, A. S., Takci, Z., Ertugrul, D. T., Bilgili, S. G., Balahoroglu, R., & Takir, M. (2015). The effect of different doses of isotretinoin on pituitary hormones. *Dermatology.*, 354-359.
- Karadag, A. S., Takci, Z., Ertugrul, D. T., Bilgili, S. G., Balahoroglu, R., & Takir, M. (2015). The effect of different doses of isotretinoin on pituitary hormones. *Dermatology*, 354-9.
- Kaymak, Y., & Ilter, N. (2006). The effectiveness of intermittent isotretinoin treatment in mild or moderate acne. *Journal of the European Academy of Dermatology and Venereology*, 1256-1260.
- Kim, M. J., Ahn, K., Park, S. H., Kang, H. J., Jang, B. G., & Oh, S. J. (2009). SIRT1 regulates tyrosine hydroxylase expression and differentiation of neuroblastoma cells via FOXO3a. *FEBS Lett*, 1183-8.
- Lafay-Chebassier, C., Chavant, F., Favreliere, S., Pizzoglio, V., Perault-Pochat, M.-C., & French Associations of Regional Centers. (2015). Drug-induced Depression: a Case/Non Case Study in the French Pharmacovigilance Database. *Therapie*, 425-432.
- Landis, M. N. (2020). Optimizing Isotretinoin Treatment of Acne: Update on Current Recommendations for Monitoring, Dosing, Safety, Adverse Effects, Compliance, and Outcomes. *Am J Clin Dermatol*, 411-419.
- Larson, M., Walker, E., & Compton, M. (2010). Early signs, diagnosis and therapeutics of the prodromal phase of schizophrenia and related psychotic disorders. *Expert Rev Neurother*, 1347-1359.
- Levenson, J. L. (1983). Biotin-responsive depression during hyperalimentation. *J Parenter Enteral Nutr*, 181-183.
- Li, C., Chen, J., Wang, W., Ai, M., Zhang, Q., & Kuang, L. (2019). Use of isotretinoin and risk of depression in patients with acne: a systematic review and meta-analysis. *BMJ Open*, e021549.
- Li, Y., Wang, Z., Kong, D., Murphy, S., Dou, Q. P., & Sheng, S. (2007). *J Biol Chem*, 21542-50.
- Lolis, M. S., Bowe, W. P., & Shalita, A. R. (2009). Acne and systemic disease. *Med Clin North Am*, 1161-1181.
- Lookingbill, D. P., Demers, L. M., Tigelaar, R. E., & Shalita, A. R. (1988). Effect of Isotretinoin on Serum Levels of Precursor and Peripherally Derived Androgens in Patients With Acne. *Arch Dermatol*, 540-543.

- Lucca, J. M., Varghese, N. A., Ramesh, M., & Ram, D. (2016). A case report of isotretinoin-induced manic psychosis. *Indian J Dermatol*, 120.
- Lynburg, M. C., Khoury, M. J., Lammer, E. J., Waller, K. O., Codero, J. F., & Erickson, J. D. (1990). Sensitivity, specificity and positive predictive value of malformations in isotretinoin embryopathy. *Teratology*, 513-519.
- Maiese, K., Chong, Z. Z., & Shang, Y. C. (2008). OutFOXing disease and disability: the therapeutic potential of targeting FoxO proteins. *Trends Mol Med*, 219-27.
- Mammucari, C., Milan, G., Romanello, V., Masiero, E., Rudolf, R., & Del, P. P. (2007). FoxO3 controls autophagy in skeletal muscle in vivo. *Cell Metab*, 458-71.
- Marron, S. E., & Tomas-Aragones, L. (2013). Anxiety, depression, quality of life and patient satisfaction in acne patients treated with oral isotretinoin. *Acta Derm Venereol*.
- McCaffery, P., & Drager, U. C. (1994). High levels of a retinoic acid-generating dehydrogenase in the meso-telencephalic dopamine system. *Proc Natl Acad Sci USA*, 7772-7776.
- McGrath, E. J., Gilson, F., Darvay, A., & Hickey, J. R. (2010). A prospective trial of the effects of isotretinoin on quality of life and depressive symptoms. *Br J Dermatol*, 1323-9.
- McGuire, J., & Lawson, J. P. (1987). Skeletal changes associated with chronic isotretinoin and etretinate administration. *Dermatologica*, 169-81.
- McMahon, R. J. (2002). Biotin in metabolism and molecular biology. *Annual Review of Nutrition*, 221-239.
- Melnik, B. C. (2011). Isotretinoin and FoxO1: a scientific hypothesis. *Dermatoendocrinol*, 141-165.
- Melnik, B. C. (2017). Apoptosis May Explain the Pharmacological Mode of Action and Adverse Effects of Isotretinoin, Including Teratogenicity. *Acta Derm Venereol*, 173-181.
- Metekoglu, S., Oral, E., Ucar, C., & Akalin, M. (2019). Does isotretinoin cause depression and anxiety in acne patients? *Dermatologic Therapy*.
- Mitchell, K. R., Geary, R., Graham, C., Clifton, S., Mercer, C. H., Lewis, R., . . . Wellings, K. (2016). Sexual Function in 16- to 21-Year-Olds in Britain. *J Adolesc Health*, 422-428.
- Molina, A. M., van der Mij, J. C., Christos, P., Wright, J., Thomas, C., Dutcher, J. P., . . . Gudas, L. G. (2020). NCI 6896: a phase I trial of vorinostat (SAHA) and isotretinoin (13-cis retinoic acid) in the treatment of patients with advanced renal cell carcinoma. *Invest New Drugs*, 1383-1389.
- Moradi Tuchayi, S., Makrantonaki, E., Ganceviciene, R., Dessinioti, C., Feldman, S. R., & Zouboulis, C. C. (2015). Acne vulgaris. *Nat Rev Dis Primers*.
- Moreau, C., Kagesten, A. E., & Blum, R. W. (2016). Sexual dysfunction among youth: an overlooked sexual health concern. *BMC Public Health*, 1170.
- Moy, A., McNamara, N. A., & Lin, M. C. (2015). Effects of Isotretinoin on Meibomian Glands. *Optometry and Vision Science*, 925-930.
- Nelson, A. M., Gilliland, K. L., Cong, Z., & Thiboutot, D. M. (2006). 13-cis Retinoic acid induces apoptosis and cell cycle arrest in human SEB-1 sebocytes. *J Invest Dermatol*, 2178-2189.

- Nelson, A., Zhao, W., Gilliland, K. L., Zaenglein, A. L., Liu, W., & Thiboutot, D. M. (2009). Temporal changes in gene expression in the skin of patients treated with isotretinoin provide insight into its mechanism of action. *Dermato-Endocrinology*, 177-87.
- Nevolarova, Z., & Dvoakova, D. (2013). Mood changes, depression and suicide risk during isotretinoin treatment: A prospective study. *Int J Dermatol*, 163-168.
- Nikam, B., Jamale, V., & Ravikumar, S. T. (2020). Effect of oral isotretinoin on anxiety and depression in patients with acne. *Journal of Pharmacology and Pharmacotherapeutics*, 113-118.
- Nikneshad, N., Hamedani, B., Zamanian, A., Robati, R. M., & Hamedani, E. (2020). Frequency of depression in patients with acne vulgaris . *Iran J Dermatol*, 150-154.
- Oberg, K., Fugl-Meyer, A. R., & Fugl-Meyer, K. S. (2004). On categorization and quantification of women's sexual dysfunctions: an epidemiological approach. *Int J Import Res.*, 261-9.
- Oliveira, J. M., Sobreira, G., Velosa, J., Correia, D. T., & Filipe, P. (2018). Association of Isotretinoin With Depression and Suicide: A Review of Current Literature. *J Cutan Med Surg*, 58-64.
- O'Reilly, K. C., Shumake, J., Gonzalez-Lima, F., Lane, M. A., & Bailey, S. J. (2006). Chronic administration of 13-cis-retinoic acid increases depression-related behavior in mice. *Neuropsychopharmacology*, 1919-1927.
- O'Sullivan, L. F., Brotto, L. A., Byers, E. S., Majerovich, J., & Wuest, J. A. (2014). Prevalence and characteristics of sexual functioning among sexually experienced middle to late adolescents. *J Sex Med*, 630-641.
- Ozkur, E., Kivanc Altunay, I., Celik, U., Sekerlisoy, G., & Falay, T. (2020). Changes of psychiatric parameters in acne patients treated with oral isotretinoin. *The Journal of Dermatology Nurses Association*.
- Ozturk, S., Ozturk, T., Ucak, H., Erden, I., Demir, B., Kayali, A., & Cicek, D. (2015). Evaluation of ovarian reserve and function in female patients treated with oral isotretinoin for severe acne: an exploratory study. *Cutan Ocul Toxicol*, 21-24.
- Quinta Gomes, A. L., & Nobre, P. J. (2014). Prevalence of sexual problems in Portugal: results of a population-based study using a stratified sample of men aged 18 to 70 years. *J Sex Res*, 13-21.
- Ra, Z., Ho, B., Bickerstaffe, L., & Bewley, A. (2020). More than skin deep: Acne vulgaris and its impact on mental health. *British Journal of Dermatology*, 13.
- Rajagopal, S. (2014). Acute psychosis induced by isotretinoin. *Indian J Psychiatry*, 295-7.
- Rastrelli, G., & Maggi, M. (2017). Erectile dysfunction in fit and healthy young men: psychological or pathological? *Transl Androl Urol.*, 79-90.
- Rea, S., Tucker, S., Frittekki, V., & Gunnarson, R. (2018). A feasibility study for a triple-blind randomised controlled trial investigating the effects of oral isotretinoin on mood and quality of life in patients with acne vulgaris. *Clinical and Experimental Dermatology*, 54-56.
- Reyna-Rodriguez, I. L., Chavez-Alvarez, S., Garza-Rodriguez, V., Franco-Marquez, R., Gonzalez-Martinez, G., Ocampo-Candiani, J., & Villarreal-Martinez, A. (2021). Cryotherapy plus low-dose oral isotretinoin vs cryotherapy only for the treatment of anogenital warts: a randomized clinical trial. *Arch Dermatol Res*.



- Reynolds, E. H., Carney, M. W., & Toone, B. K. (1984). Methylation and mood. *Lancet*, 196-198.
- Reynolds, O. (1991). Erectile dysfunction in etretinate treatment. *Arch Dermatol.*, 425-425.
- Richters, J., Grulich, A. E., de Visser, R. O., Smith, A. M., & Rissel, C. E. (2003). Sex in Australia: sexual difficulties in a representative sample of adults. *Aust N Z J Public Health*, 164-170.
- Rioux, L., & Arnold, S. E. (2005). The expression of retinoic acid receptor  $\alpha$  is increased in the granule cells of the dentate gyrus in schizophrenia. *Psychiatry Res*, 13-21.
- Rossi, M., & Pellegrino, M. (2009). Acitretin-associated erectile dysfunction: A case report. *Cases Journal*, 210.
- Sadek, I. A., & Abdul-Mohsen, M. H. (1999). Long-term administration of vitamin A and the process of spermatogenesis. *East Mediterr Health J*, 123-129.
- Sakai, Y., Crandall, J. E., Brodsky, J., & McCaffery, P. (2004). 13-cis retinoic acid (Accutane) suppresses hippocampal cell survival in mice. *Ann NY Acad Sci*, 436-440.
- Sakoe, Y., Sakoe, K., Kirito, K., Ozawa, K., & Komatsu, N. (2010). FOXO3A as a key molecule for all trans retinoic acid induced granulocytic differentiation and apoptosis in promyelocytic leukemia. *Blood*, 3787-95.
- Salmon, N., Affleck, A., Nicolson, J., & Stewart, A. (2019). Mental health concerns in patients taking isotretinoin for acne: A survey of dermatologists and implications for future practice. *British Journal of Dermatology*.
- Salposky, R. M. (2001). Depression, antidepressants and the shrinking hippocampus. *Proc Natl Acad Sci*, 12320-12322.
- Samad, T. A., Krezel, W., Chambon, P., & Borrelli, E. (1997). Regulation of dopaminergic pathways by retinoids: activation of the D2 receptor promoter by members of the retinoic acid receptor-retinoid X receptor family. *Proc Natl Acad Sci USA*, 14349-14354.
- Sandri, M., Sandri, C., Gilbert, A., Skurk, C., Calabria, E., & Picard, A. (2004). Foxo transcription factors induce the atrophy related ubiquitin ligase atrogin-1 and cause skeletal muscle atrophy. *Cell*, 399-412.
- Sardana, K., & Garg, V. K. (2010). Efficacy of low-dose isotretinoin in acne vulgaris. *Indian J Dermatol Venereol Leprol*, 7-13.
- Schmidt, J. B., Spona, J., & Huber, J. (1986). Androgen receptor in hirsutism and acne. *Gynecologic and Obstetric Investigation*, 206-211.
- Schulpis, K. H., Georgala, S., Papkonstantinou, E. D., Michas, T., & Karikas, G. A. (1999). The effect of isotretinoin on biotinidase activity. *Skin Pharmacol Appl Skin Physiol.*, 28-33.
- Schulpis, K. H., Karikas, G. A., Georgala, S., Michas, T., & Tsakiris, S. (2001). Elevated plasma homocysteine levels in patients on isotretinoin therapy for cystic acne. *Int J Dermatol*, 33-36.
- Scott, D. (1958). Clinical biotin deficiency ("egg white injury"): Report of a case with some remarks on serum cholesterol. *Acta Med Scand*, 162.
- Silverman, A. K., Ellis, C. N., & Voorhees, J. J. (1987). Hypervitaminosis A syndrome: a paradigm of retinoid side effects. *J Am Acad Dermatol.*, 1027-1039.

- Simic , D., Penavic, J. Z., Babic, D., & Gunaric, A. (2017). Psychological status and quality of life in acne pateints treated with oral isotretinoin. *Psychiatr Danub*, 104-110.
- Singer, S., Tkachenko, E., Sharma, P., & Barbieri, J. S. (2019). Psychiatric Adverse Events in Patients Taking Isotretinoin as Reported in a Food and Drug Administration Database From 1997 to 2017. *JAMA Dermatology*, 1162-66.
- Smithard, A., Glazebrook, C., & Williams, H. C. (2001). Acne prevalence, knowledge about acne and psychological morbidity in mid-adolescence: a community-based study. *British Journal of Dermatology*, 274-279.
- Smithard, C. G. (2001). Acne prevalence, knowledge about acne and psychological morbidity in mid-adolescence: a community based study. . *British Journal of Dermatology*.
- Solmi, F., Hotopf, M., Hatch, S. L., Treasure, J., & Micali, N. (2016). Eating disorders in a multi-ethnic inner-city UK sample: prevalence, comorbidity and service use. *Soc Psychiatr Epidemiol*, 369-81.
- Soundararajan, V., Ali, Y., Majeswki, S., Ruack, C., Jimenez, J., Puar, N., . . . Nardone, B. (2020). Prevalence of depression in patients being managed for acne: Analysis of a large midwestern U.S. dermatology population from the radar (Research On Adverse Drug Events And Reports) program. *Journal of the Dermatology Nurses' Association*.
- Suarez , B., Serrano, A., Cova, Y., & Baptista , T. (2016). Isotretinoin was not associated with depression or anxiety: A twelve-week study. *World J Psychiatry*, 136-142.
- Sutaria, A. H., Masood, S., & Schlessinger, J. (2021). Acne Vulgaris. *tatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan*.
- Sweeting , H., Walker, L., MacLean, A., Patterson, C., Raisanen, U., & Hunt , K. (2015). Prevalence of eating disorders in males: a review of rates reported in academic research and UK mass media. *Int J Mens Health*.
- Sweetman, L., Surh, L., Baker , H. P., & Nyhan, W. L. (1981). Clinical and metabolic abnormalities in a boy with dietary deficiency of biotin. *Paediatrics*, 553-558.
- Sydenstricker, V. P., Singal, S. A., Briggs, A. P., DeV Vaughn, N. M., & Isbel, H. (1942). Observations on the“egg white injury” in man and its cure with a biotin concentrate. *JAMA*, 1199.
- Tan, J. K., & Bhate, K. (2015). A global perspective on the epidemiology of acne. *Br J Dermatol*, 3-12.
- Thioboutot, D. M., Dreno, B., Abanmi, A., & et al. (2018). Practical management of acne for clinicians: An international consensus from the Global Alliance to Improve Outcomes in Acne. *J Am Acad Dermatol*.
- Tirado Sanchez, A., & Leon Dorantes, G. (2005). Erectile dysfunction during isotretinoin therapy. *Actas Urol Esp.*, 974-976.
- Truitt, J. M., Reichenberg, J. S., Shargi, K. G., Sampson, S. M., Reonigk, R. K., & Magid, M. (2018). Isotretinoin: the ups are just as troubling as the downs. *G Ital Dermatol Venereol*, 535-539.
- Ugonabo, N., Love, E., Wong, P. W., Rieder, E. A., Orlow, S. J., Kim, R. H., & Nagler, A. R. (2021). Psychiatric disorders and suicidal behavior in patients with acne prescribed oral antibiotics versus isotretinoin: Analysis of a large commercial insurance claims database. *J Am Acad Dermatol*, 878-884.

- Vaidya, V. A., Fernandes, K., & Jha, S. (2007). Regulation of adult hippocampal neurogenesis: relevance to depression. *Expert Rev Neurother*, 853-864.
- Vallerand, I. A. (2018). Risk of depression among patients with acne in the UK: a population based cohort study. *Br J Dermatol*, e194-e195.
- Williams, H. C., Dellavalle, R. P., & Garner, S. (2012). Acne vulgaris. *Lancet*, 361-72.
- Wood, S., Marchant, A., Allsop, M., Wilkinson, K., Bethel, J., Jones, H., & John, A. (2019). Epidemiology of eating disorders in primary care in children and young people: a Clinical Practice Research Datalink study in England. *BMJ Open*, bmjopen-2018-026691.
- Wysowski, D. K., & Swartz, L. (2005). Relationship between headache and depression in users of isotretinoin. *Arch Dermatol*, 640-641.
- Yap, F. B. (2017). Safety and efficacy of fixed dose 10mg daily isotretinoin treatment for acne vulgaris in Malaysia. *J of Cosmetic Derm*, 348-352.
- Yentzer, B. A., Hick, J., Reese, E. L., Uhas, A., Feldman, S. R., & Balkrishnan, R. (2010). Acne vulgaris in the United States: a descriptive epidemiology. *Cutis*, 94-9.
- Zakheim, G., Goldberg, J., Motosko, C., Cohen, B., & Ho, R. (2019). Sexual dysfunction in men taking systemic dermatologic medication. *JAAD*, 163-172.
- Zhao, J., Brault, J. J., Schild, A., Cao, P., Sandri, M., & Schiaffino, S. (2007). FoxO3 coordinately activates protein degradation by the autophagic/lysosomal and proteasomal pathways in atrophying muscle cells. *Cell Metab*, 472-83.
- Zipfel, S., Giel, K. E., Bulik, C. M., Hay, P., & Schmidt, U. (2015). Anorexia nervosa: aetiology, assessment, and treatment. *The Lancet Psychiatry*.

## **ANNEX 1: Call For Information**

### **Promotion of the call for information**

Details about the isotretinoin review and the call for information were published on the GOV.UK website. Individual emails highlighting the call for information were circulated to relevant stakeholders including patients and their families who had previously raised concerns about isotretinoin. Relevant healthcare organisations were asked to share the information with their members.

The MHRA's bulletin Drug Safety Update<sup>46</sup> which is distributed to healthcare professionals in the UK, included an article in the November 2020 edition about contributing to the expert review.

The review was also promoted on social media including Twitter, Facebook, Instagram and LinkedIn. This included using paid-for social media to target relevant patients and healthcare professionals to widen the awareness and improve responses.

The information campaign to promote the call for information led to 710 completed responses, which is a high response rate compared with previous similar exercises conducted by MHRA.

Responders to the call for information were asked to indicate how they heard about the review. No restrictions were applied to the number of sources and some responders indicated multiple sources including direct communication as well as word of mouth or social media. Responders most commonly heard about the review via social media (50%) or "other" sources which included word of mouth, online searches on isotretinoin, prescribers or pharmacists directly informing patients and their families.

### **Responses received**

A total of 710 complete responses were received. These included 659 responses that provided views and the remaining 51 registered their interest in only receiving updates about the review without providing any additional information.

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<sup>46</sup> <https://www.gov.uk/drug-safety-update/isotretinoin-roaccutane-reminder-of-important-risks-and-precautions>

Figure 1. Summary of responders to the call for information

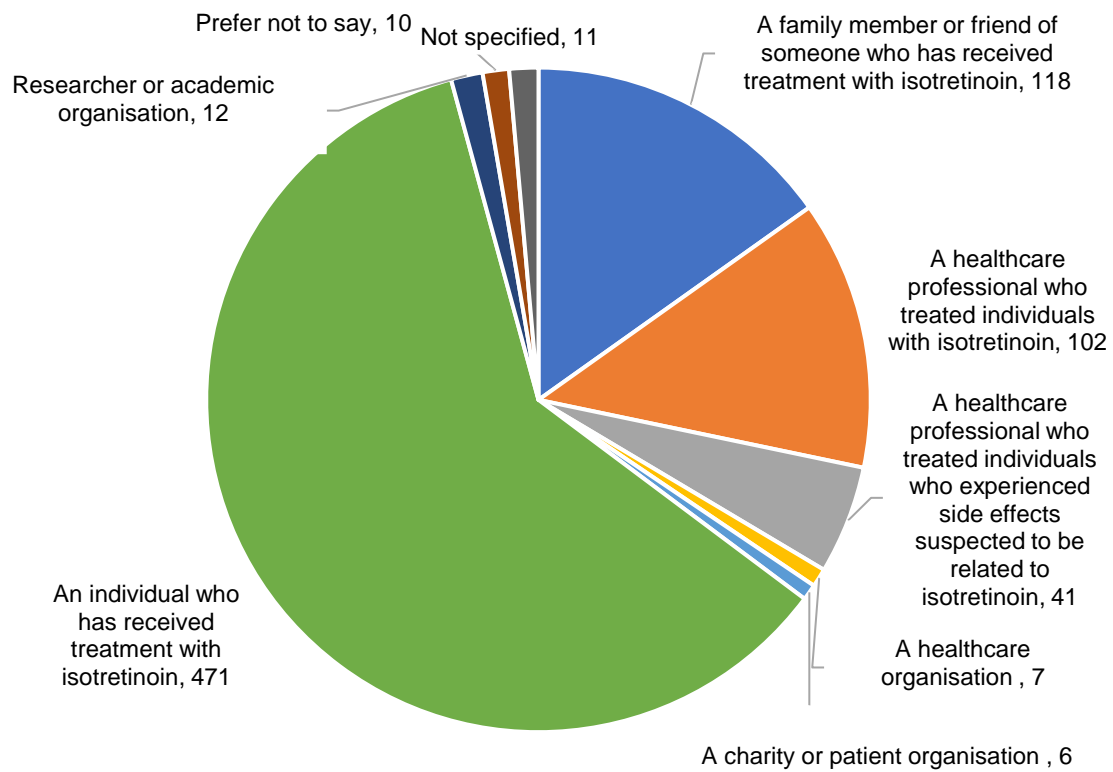


Figure 1 provides a summary of the stakeholders who responded to the call for information. Responders could select all of the categories which applied; therefore, the same individual may be included in multiple categories such as an individual who has received isotretinoin as well as a family member or friend of someone who has received isotretinoin. It is also important to note that the patient and their friends or family may also have submitted separate responses to express their views and experience of the same treatment course with isotretinoin.

Responders were asked to indicate their overall view of isotretinoin from positive, negative, both/other. Only 3 responders did not complete this part and figure 2 provides a summary of this information.

Figure 2. Summary of the overall views of stakeholders on isotretinoin

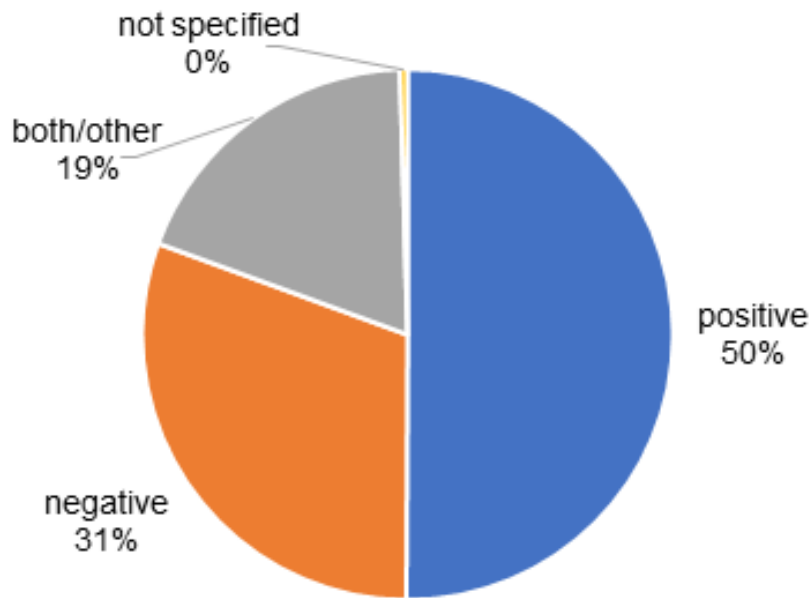
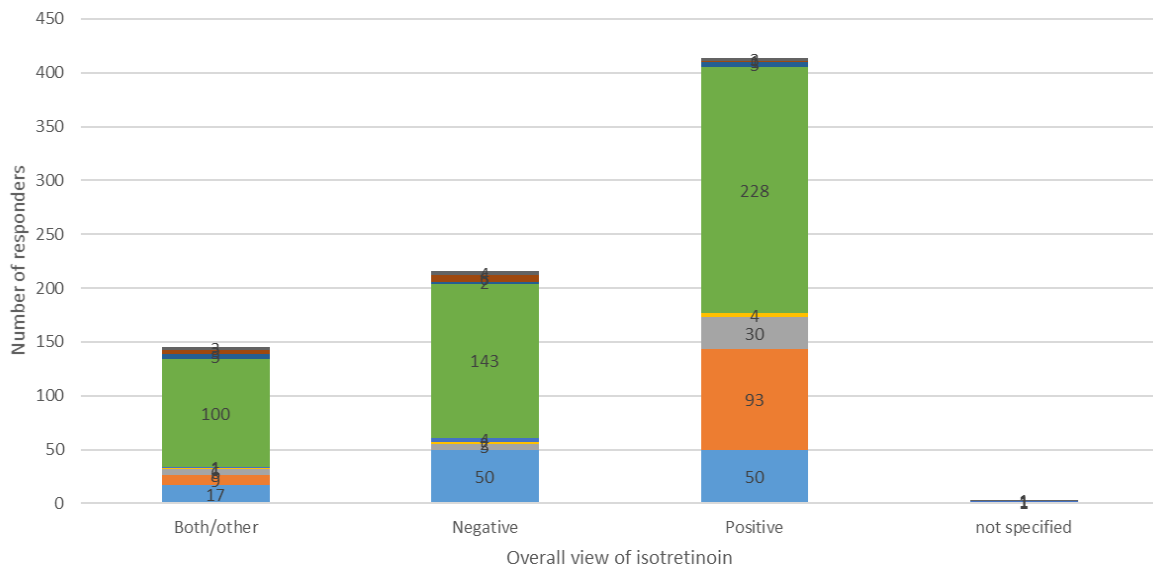


Figure 3. Breakdown of overall views by responder category

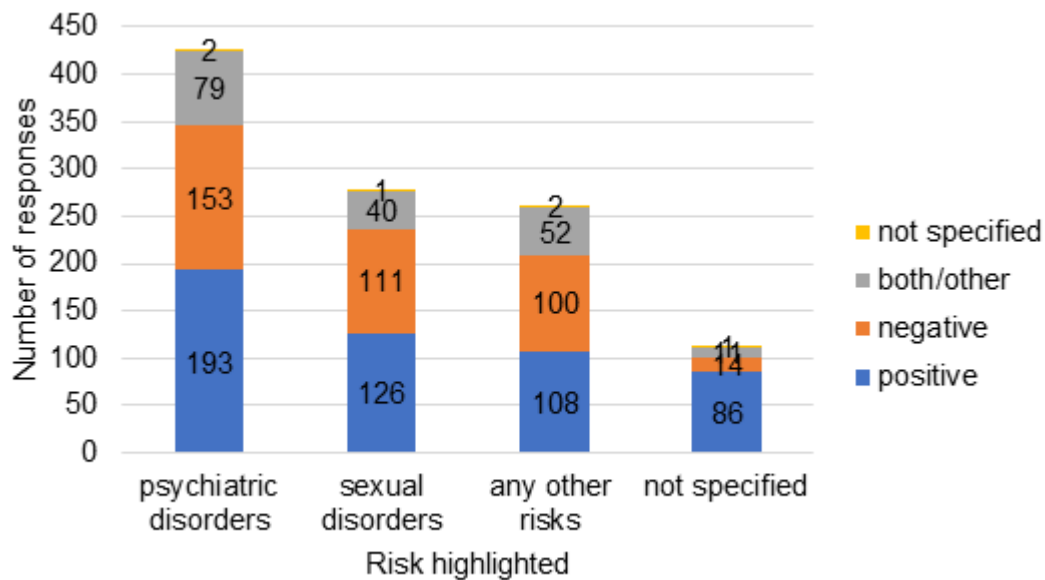


- Not specified
- Prefer not to say
- Researcher or academic organisation
- An individual who has received treatment with isotretinoin
- A charity or patient organisation
- A healthcare organisation
- A healthcare professional who treated individuals who experienced side effects suspected to be related to isotretinoin
- A healthcare professional who treated individuals with isotretinoin
- A family member or friend of someone who has received treatment with isotretinoin

Figure 3 provides a breakdown of the responder categories for each of the groups outlined in Figure 2. Individuals who were treated with isotretinoin are represented in the positive, negative and neutral groups. However, healthcare professionals generally had positive views on isotretinoin.

Each responder was asked to indicate whether they had views on psychiatric disorders, sexual disorders or any other risks. No restrictions were placed on the number of areas that could be selected with individuals selecting between none and all three options. Figure 4 provides a summary of the risks selected by overall view on isotretinoin.

Figure 4. Summary of risks by views expressed



It is worth noting that regardless of the individuals' overall view on isotretinoin, responders generally had views on the risks. Further discussion of the views on each risk are provided in subsequent sections of this paper.

The call for information gathered views on the current measures in place to minimise the risks associated with isotretinoin and whether additional measures are needed. Figure 5 provides a summary of the responses on the need for additional measures.

Figure 5. Summary of the responses on the need for additional measures

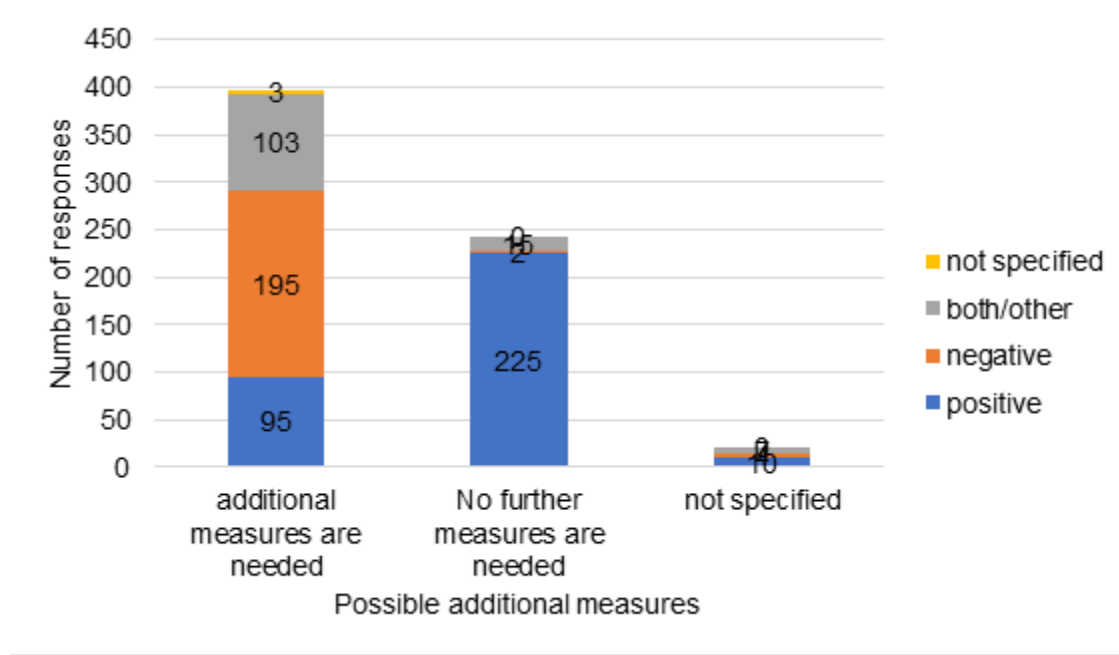
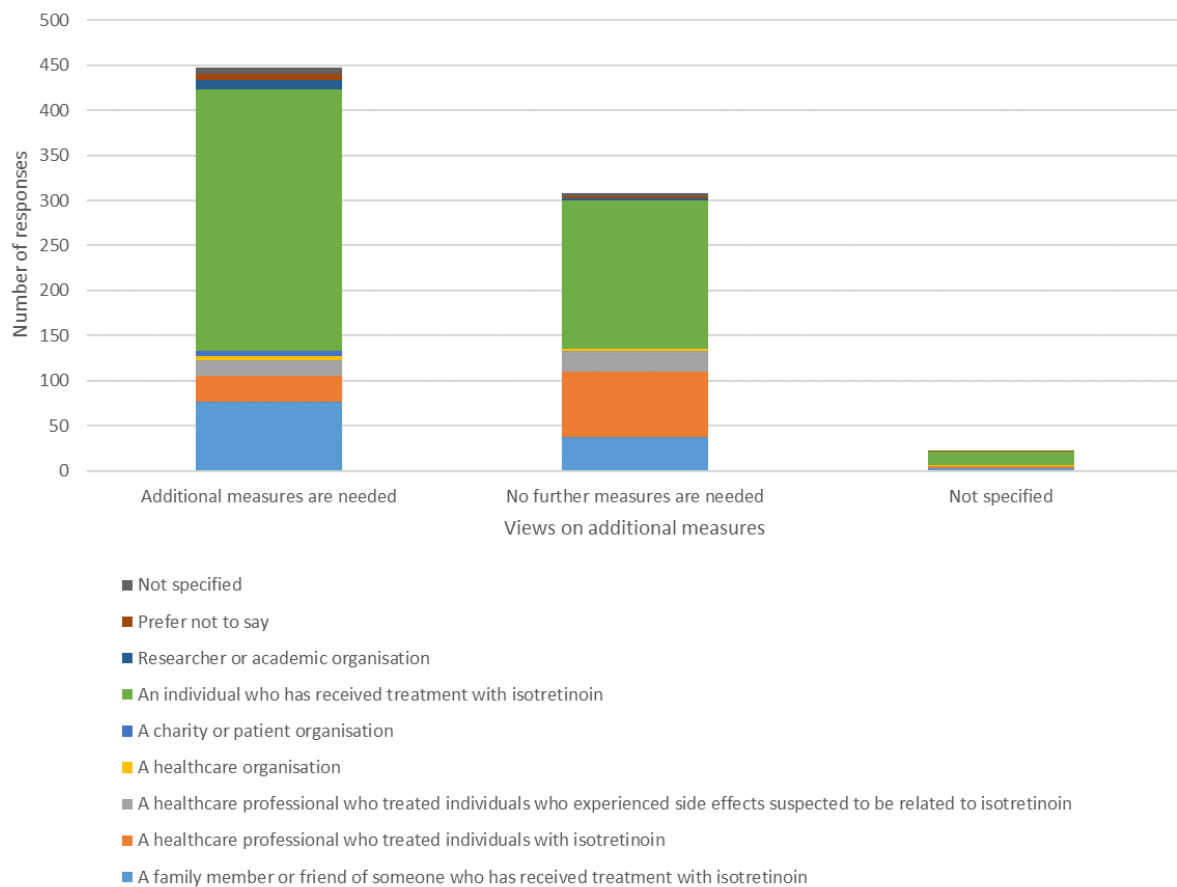


Figure 5 indicates that the majority of responders who have a negative view about isotretinoin indicated that additional measures are needed whereas the majority of those with a positive view of isotretinoin did not consider further measures to be needed. Figure 6 provides a breakdown of the responder category in relation to their views on whether additional risk minimisation measures are needed.



Figure 6. Breakdown of views on additional risk minimisation measures by responder category



There were challenges with interpreting the responses from the call for information. It was impossible to determine how representative responders were of all users. The call may have attracted people with particularly bad experiences / strongly held views and so the frequency of risks and benefits could not be estimated. Also, some responders came from overseas where regulations for prescribing isotretinoin may differ from those in the UK. Nevertheless, the data provided very valuable insights into the range and severity of difficulties experienced as well as positive experiences that are usually not recorded in side effect reporting systems. This empirical data provided a more representative sample than the Yellow Card data (described later in the report), which provides information on side effects alone. This may, therefore, provide a more generalisable stakeholder experience. However, this descriptive data describes experiences and events but lacks pertinent demographic information and clinical data necessary to make causal associations with isotretinoin.

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