Medicines & Healthcare products Regulatory Agency

Review of the implementation of the recommendations of the Commission on Human Medicines Isotretinoin Expert Working Group and Isotretinoin Implementation Advisory Expert Working Group.

Public Assessment Report

Medicines and Healthcare products Regulatory Agency

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Contents

1. Plain Language Summary

Key messages:

The Commission on Human Medicines (CHM) has reviewed the current measures in place for the prescribing of isotretinoin. Following the review, the CHM has advised several changes[1] which are outlined below.

Follow-up consultations guidance

The CHM has advised changes to the Isotretinoin Implementation Advisory Expert Working Group (IIAEWG) recommendations that follow-up consultations do not necessarily need to be in person (face to face) and could be remote if appropriate. This should be discussed and agreed with the patient and should take into account the clinical assessment, the patient's needs and preferences, and safeguarding considerations. Prescribers should be mindful of professional standards and best practice e.g. General Medical Council (GMC) guidance, guidance from professional bodies, and other relevant guidelines and local polices. The British Association of Dermatologists (BAD) will also be providing clinical guidance on consultations as the professional body.

Remote pregnancy testing guidance

The CHM advised that remote pregnancy testing may be regarded as a medically supervised test with appropriate guidance and oversight, to ensure tests are performed correctly and safely. This recommendation was conditional on regular clinical audits led by the BAD to monitor compliance to the Summary of Product Characteristics (SmPC), and for the BAD to develop clinical guidance on remote pregnancy testing. The BAD clinical guidance on remote pregnancy testing for healthcare professionals is signposted in the addendum to the IIAEWG report.

Sexual function monitoring

The CHM advised that patients should be asked about sexual function at follow up appointments, although by the third appointment, this may be brief and could be aided by use of a questionnaire before the consultation. This monitoring was

[1] Updates to follow-up consultations guidance, remote pregnancy testing guidance, and sexual function monitoring were communicated in a Drug Safety Update (DSU) on 27 October 2025.

considered particularly important since the timeframe of onset of sexual function side effects is not known and has been reported to persist after treatment has completed. The BAD has developed clinical guidance on sexual function monitoring which is signposted in the addendum to the IIAEWG report.

Second Prescriber in patients under 18 years of age

To inform the CHM recommendations on the regulatory requirements of isotretinoin, and in particular the second prescriber, the MHRA asked all dermatology services who prescribe isotretinoin to complete a survey regarding their service by 16 November 2025.

Following a review of this survey, and in response to evidence that the second prescriber regulatory requirement is reducing capacity and leading to potential delays to treatment (which may increase the risk of scarring), together with noted structural changes to clinical pathways, the CHM advised replacing the second prescriber with a range of additional measures.

The additional measures that are being introduced include:

1) Updates to the risk acknowledgment form for all patients:

a) to confirm that the patient understands the therapeutic indication of isotretinoin, and for the prescriber to confirm that isotretinoin is clinically indicated for the patient and that there is no other appropriate effective treatment.

b) to offer patients a second opinion

c) the form will be streamlined to fit two pages

2) A clinical audit of risk minimisation measures has been developed, which will be implemented by the BAD.

3) A patient information video produced by the BAD to explain the risks associated with isotretinoin treatment in another format, which is more easily accessible to some patients.

Further regulatory action will be considered if adherence to the risk minimisation measures is not sustained, as evidenced by data from the clinical audits.

More information about this medicine

Isotretinoin is an effective treatment for severe forms of acne (such as nodular or conglobate acne, or acne at risk of permanent scarring) which has not responded to adequate courses of standard therapy with systemic anti-bacterials and topical therapy.

All medicines have benefits and risks. Isotretinoin works well to treat severe acne, but it can cause side effects. Some side effects may continue even after stopping isotretinoin. We do not know how often this happens, or how long those side effects can last.

Isotretinoin can seriously harm an unborn baby. This is why patients must not become pregnant during treatment with isotretinoin and for 1 month after isotretinoin is stopped. Patients of childbearing potential (anyone who may be able to get pregnant) must enter the Pregnancy Prevention Programme.

Before starting isotretinoin patients need to complete an Isotretinoin Acknowledgement of Risk Form with their prescriber in order to make sure that they are aware about the side effects and possible risks which have been associated with isotretinoin.

Reasons for the latest review and information considered

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. The CHM therefore convened an Isotretinoin Expert Working Group (IEWG) in September 2019 to review the association between isotretinoin, severe acne, mental health and sexual function. 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. The CHM recognised that implementation would require changes in

organisational structures, regulatory advice, and clinical care and therefore set up a multi-disciplinary Isotretinoin Implementation Advisory Expert Working Group (IIAEWG), to advise on the best way to implement the recommendations.

This Public Assessment Report reviewed implementation of these recommendations of the CHM IIAEWG.

Advice from CHM

Following the implementation of the recommendations of the CHM IEWG and IIAEWG in 2023, the MHRA has conducted a review of the implementation of these measures and has sought advice from CHM. The CHM considered and advised on issues associated with the implementation of the new regulatory requirements for isotretinoin after considering all the available data. The CHM noted:

i. Structural changes to clinical pathways in response to the IIAEWG report have been made by healthcare professionals, supported by the BAD, to improve the counselling of patients in order that they are fully informed of the benefits and risks of isotretinoin prior to starting treatment, and to ensure consistent monitoring for any side effects.

ii. Ongoing concerns about private practice as there is evidence that some prescribing in the private sector does not adhere to the regulatory requirements and IIAEWG guidance. The lack of data sources from private providers limits understanding in this sector which is being used increasingly by patients to access treatments such as isotretinoin, due to the long-standing waiting times for dermatology appointments.

iii. Some evidence that the requirement for two prescribers is leading to a reduced capacity and access. This evidence includes questionnaire data from the BAD members and an NHS England impact assessment, both of which have limitations.

The purpose for the introduction of two prescribers in this population was for greater oversight in patients under the age of 18, to confirm that treatment was appropriate and that patients had the therapeutic indication of severe acne resistant to adequate courses of standard therapy. The CHM noted that the data provided by the BAD illustrates very little disagreement between the two prescribers and the limited treatment options for severe acne; therefore it is not

clear how much additional safety is gained from a second prescriber. Balanced against this, there is now some evidence that the requirement for two prescribers is leading to a reduced capacity and access, exacerbating delays to treatment which could lead to harm through an increased risk of scarring and other associated consequences of acne.

Second Prescriber

The CHM reviewed the requirement for patients under 18 years of age, which stipulates that two independent prescribers must agree there is no other appropriate effective treatment before initiating isotretinoin therapy. The evidence suggested that the requirement is reducing capacity and leading to potential delays to treatment, which could increase the risk of harm. The data provided by the BAD also illustrated very little disagreement between clinicians, and noting the limited treatment options for severe acne, suggesting that the involvement of a second prescriber offers limited additional safety benefits. The CHM considered additional risk minimisation measures that could be implemented to replace two prescribers, whilst ensuring the safety of isotretinoin prescribing.

The outcome of this evaluation was that the CHM advised removing the second prescriber requirement in light of the evidence regarding possible access issues and evidence there was little disagreement between the two prescribers, provided additional risk mitigation measures are in place.

The additional risk mitigation measures introduced to include:

1) Changes to the risk acknowledgment form for all patients:

a) to confirm that the patient understands the therapeutic indication of isotretinoin, and the prescriber to confirm that isotretinoin is clinically indicated for the patient and that there is no other appropriate effective treatment.

b) to offer all patients a second opinion

c) reference to watching a patient information video

d) the form will also be streamlined to fit two pages

2) A clinical audit of risk minimisation measures developed and implemented by the BAD. If there is evidence of poor practice, other regulatory measures will be considered by the CHM.

3) A patient information video has been produced by the BAD to explain the risks associated with isotretinoin treatment in another format, more easily accessible to some patients. This is referenced in the updated Acknowledgment of Risk Form.

These measures aim to improve the safe prescribing of isotretinoin and strengthen the ability to monitor safe prescribing, whilst supporting patient access to treatment.

Follow-up consultations guidance

The CHM has advised changes to the IIAEWG recommendations that follow-up consultations do not necessarily need to be in person (face to face) and could be remote if appropriate. It was emphasised that this should be discussed and agreed with the patient and should take into account the clinical assessment, the patient's needs and preferences, and safeguarding considerations. Prescribers should be mindful of professional standards and best practice e.g. General Medical Council (GMC) guidance, guidance from professional bodies, and other relevant guidelines and local polices. The BAD has provided clinical guidance on this topic.

Remote pregnancy testing guidance

The CHM advised that remote pregnancy testing may be regarded as a medically supervised test with appropriate guidance and oversight, to ensure tests are performed correctly and safely. The CHM advised that this recommendation was conditional on regular clinical audits led by the BAD to monitor compliance to the SmPC and for the BAD to develop clinical guidance on remote pregnancy testing. The BAD has developed clinical guidance on remote pregnancy testing for healthcare professionals.

Sexual function monitoring

The CHM advised that patients should be asked about sexual function at follow up appointments, although by the third appointment, this may be brief and could be aided by use of a questionnaire before the consultation. CHM noted this monitoring was particularly important as the timeframe of onset of sexual function

side effects is not known and has been reported to persist after treatment has completed. The BAD has developed clinical guidance on sexual function monitoring.

Next steps

Additional new risk mitigation measures (not regulatory) will be introduced including, a new patient information video developed by the BAD, and introduction of a new clinical audit of dermatology services by the BAD about the prescribing of isotretinoin which will be overseen by the MHRA. Other changes include updates to the IIAEWG recommendations that follow-up consultations do not necessarily need to be in person (face to face) and could be remote if appropriate, and that medically supervised pregnancy testing in isotretinoin treatment could be performed remotely.

Following further advice from CHM regarding the second prescriber, the Manufacturing Authorisation Holders (MAHs) for isotretinoin have removed the requirement for a second prescriber for the initiation of isotretinoin treatment for severe acne in patients under 18 years of age. This includes changes to the product information (SmPC, and Patient Information Leaflet) and Risk Minimisation Materials - Acknowledgement of Risk form. The Acknowledgement of Risk form has been streamlined, questions on seeking a second opinion and confirming the patients understanding of the therapeutic indication have been added.

Drug Safety Updates will be published in addition to this Public Assessment Report to communicate these changes to health care professionals.

2. Introduction

The MHRA is the regulator of medicines, medical devices and blood components for transfusion in the UK. The MHRA is responsible for making sure these products meet acceptable standards for safety, quality and efficacy. The CHM advises the government about medicines safety. The CHM is independent – it is not part of the government or the pharmaceutical industry.

In our safety Public Assessment Reports, we discuss evidence-based assessments of safety issues associated with a particular medicine or group of medicines.

The CHM and its IEWG published their independent report in April 2023.The CHM and its IEWG was asked to consider whether further regulatory action was required 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. A number of recommendations were made with the aim of improving the safety of isotretinoin for the treatment of acne.

The CHM recognised that implementation of the recommendations in the IEWG report would require changes in organisational structures, regulatory advice, and clinical care. They therefore set up a multi-disciplinary IIAEWG, to advise on the best way to implement the recommendations. The report of The IIAEWG was published in October 2023.

This Public Assessment Report presents the MHRA's review of implementation of the recommendations of the CHM IEWG and IIAEWG and the corresponding advice of CHM. Changes have been made to the ordering and wording used in the original assessment report to aid readability and presentation.

A glossary is provided for an explanation of the terms used in this report.

The information and analyses contained in this report reflect evidence that was available at the time of the review in February 2025. The MHRA and CHM will continue to monitor the safety of isotretinoin closely, however the information in this report will not be actively updated with new data or studies.

3. Background

3.1 Isotretinoin

Isotretinoin (13-cis-retinoic acid) has been authorised in the UK since 1983 for the treatment of severe forms of acne, such as nodular or conglobate acne or acne at risk of permanent scarring, and resistant to adequate courses of standard therapy with systemic antibacterials and topical therapy.

The exact mechanism of action of isotretinoin for the treatment of acne has not been fully elucidated; however, it has been established that isotretinoin has wide-ranging activity on a number of physiological pathways. 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, cellular differentiation, proliferation and apoptosis. The CHM IEWG report has further details of mechanisms of action for therapeutic effect.

While isotretinoin is a highly efficacious treatment for acne it is known to be highly teratogenic and can cause a range of other side effects. Patients and members of the public have consistently raised concerns about psychiatric and sexual function side effects suspected to be associated with isotretinoin, including those that may persist after the discontinuation of treatment.

3.2 CHM Isotretinoin Expert Working Group (IEWG) and Isotretinoin Implementation Expert Advisory Group (IIEAWG)

3.2.1 CHM IEWG review (April 2023 report)

The Government's independent advisory committee, the CHM reconvened the IEWG 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 IEWG had last met in July 2014 to consider psychiatric side effects suspected to be associated with the use of isotretinoin. The IEWG reviewed all the available latest evidence on the risk of psychiatric and sexual side effects associated with isotretinoin including reports and testimonials from patients or their families. The CHM IEWG report was published in April 2023.

3.2.2 IEWG Report Stakeholder Views Summary (April 2023 report)

The following themes were raised repeatedly in the call for information, written contributions and presentations. These are described more fully in the IEWG report published in 2023. 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. Patient experience varied between clinics, suggesting a more consistent approach was needed to ensure patients and their families know what to expect and are able to 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. There was particular concern about the lack of awareness of sexual side effects and of the potential long-term nature of some side effects. Some stakeholders felt that isotretinoin was prescribed inappropriately (to those who did not have severe acne or who had not failed other treatments) 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, as well as a lack of support for people experiencing side effects. Some stakeholders did not consider isotretinoin safe enough to be prescribed to any patients. Other stakeholders raised concerns about whether isotretinoin was suitable for use in younger patients who may not fully understand the risks and called for restrictions on its use in those under the age of 18 years. Conversely, some 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.

The lived experience gained through the stakeholder engagement exercise provided a more diverse range of views than can be obtained through simply examining the Yellow Card data, which provided information on side effects alone. There were 659 completed responses received for the call for information. Not all responses expressed a view on whether they thought isotretinoin was positive or negative but out of those who expressed a view, 50% communicated only positives views; 31% communicated only negative views and 19% communicated both positive and negative views or other views.

3.2.3 IEWG report themes (April 2023 report)

The review's conclusions and recommendations are as follows with further details within the IEWG report[2].

The key themes identified included:

- Data limitations meaning 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 excluded, and the individual experiences of patients and families continue to raise concern.

- Better information needed on side effects to support informed decision making.

- Further information on frequency of psychiatric side effects for patients to understand the uncertainty in this risk and its likely order of magnitude.

- Awareness of the risk of side effects continuing long term.

- Screening and monitoring of patients.

- Restriction of use of isotretinoin based on age.

- Informed decision making.

- Dosing guidance.

- 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.

- The need for further research.

[2] Medicines and Healthcare products Regulatory Agency. Report of the Commission on Human Medicines Isotretinoin Expert Working Group. Published 26 April 2023. Accessed by MHRA 2 February 2025.

3.2.4 Recommendations of the CHM (April 2023 report)

The CHM considered the evaluation and report of the IEWG and made a number of recommendations with the aim of improving the safety of isotretinoin for the treatment of acne. This included improvements to the product information on potential risks, consistent monitoring of possible side effects, and additional oversight of the initiation of treatment for patients under 18 years of age.

The CHM recommendations were as follows:

- Changes to product information to include warnings about the potential for sexual side effects, changing the frequency of psychiatric side effects to ‘not known’, undertaking an initial assessment of mental health status and counselling about the possible risk of mental health and sexual function side effects.

- Updates to the Acknowledgment of Risk form to cover all potential risks which should be used for all patients.

- 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.

- Consideration of the roles and responsibilities of healthcare professionals.

- Consideration of further research.

3.2.5. CHM IIAEWG (October 2023 report)

The CHM recognised that implementation would require changes in organisational structures, regulatory advice, and clinical care and therefore set up a multi-disciplinary IIAEWG, to advise on the best way to safely embed the recommendations. Membership of the group included those with expertise in dermatology, general practice, paediatrics and psychiatry (including child and

adolescent psychiatry), psychology, nursing, and pharmacy. In addition, there was a lay member. The Chair was a consultant dermatologist. The report of CHM IIAEWG[3] was published in October 2023.

The CHM IIAEWG recommendations outlined in the report also formalised some existing prescribing practices and endeavoured to reduce variation in practice, to support appropriate prescribing. Some CHM IIAEWG recommendations included suggestions on good clinical practice approaches, such as the use of face-to-face consultations. These recommendations are outside the regulatory remit of the MHRA and therefore were not introduced as regulatory requirements within the SmPC) regulatory updates. To support implementation, additional guidance was introduced, including that produced by the BAD. This included templates of example referral proformas and a side effects questionnaire which could be modified for local use. The CHM IIAEWG report included guidance covering:

a) Isotretinoin prescribing

i. Defining which healthcare professionals have the skills and expertise to be suitable prescribers of isotretinoin.

   This guidance was deemed to be necessary because 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 was historically interpreted to mean isotretinoin should be prescribed by, or under the supervision of, a consultant dermatologist. As healthcare services have evolved and new healthcare professional (HCP) roles have developed, a wider group of HCPs are prescribing isotretinoin in secondary care, community services and the private sector, with significant variability in practice across the UK.

ii. The role of the Lead Prescriber (the HCP who makes the decision to initiate isotretinoin).

[3] Medicines and Healthcare products Regulatory Agency. Report of The Commission on Human Medicines Isotretinoin Implementation Advisory Expert Working Group. Published 31 October 2023. Updated 8 February 2024. Updated 27 October 2025.

iii. The role of the Second Approved Named HCP, for adolescents under 18 years old (the HCP who agrees that there is no other appropriate effective treatment before initiation of isotretinoin therapy).

iv. The means by which the Second Approved Named HCP can independently assess the patient. This will depend on individual circumstances and prescribers. Options include:

- in person (face to face) assessment
- remote assessment by telephone (with images) or video consultation
- review of patient history and examination findings in a multi-disciplinary team (MDT) meeting (with images). If the Lead Prescriber is present at the MDT, then images may not be required.

v. Defining which healthcare professionals are suitable prescribers for the continuation and monitoring of isotretinoin treatment.

b) Mental health framework

i. Information provision and counselling

ii. How to conduct the initial mental health assessment and ongoing monitoring of mental health at follow-up appointments during isotretinoin treatment.

c) Sexual function framework

i. Information provision and counselling

ii. Initial sexual function assessment and ongoing monitoring of sexual function at follow-up appointments during isotretinoin treatment.

d) Revised Acknowledgement of Risk form with changes to the Pregnancy Prevention Programme.

A Pregnancy Prevention Programme has been in place for isotretinoin for many years due to its highly teratogenic properties. Its use is associated with a high frequency of severe and life-threatening birth defects including central nervous system abnormalities (hydrocephalus, cerebellar

malformation/abnormalities, microcephaly), cardiovascular abnormalities (conotruncal malformations such as tetralogy of Fallot, transposition of great vessels, septal defects) and an increased incidence of spontaneous abortion.

Although the IEWG recommendations did not consider the Pregnancy Prevention Programme, as this was outside the scope of the review, the IIAEWG recommended changes to the Pregnancy Prevention Programme section of the Acknowledgement of Risk form as many dermatologists did not use the pre-existing Acknowledgement of Risk form for prescribing isotretinoin to female patients.

The Acknowledgment of Risk form introduced some flexibilities e.g. no contraception required when there is expected to be no risk of pregnancy during treatment and no risk for 1 month after treatment. It also included a change in recommendations for patients on highly effective forms of contraception where they would no longer require monthly pregnancy tests. This was in line with the CHM guidance regarding medicines with teratogenic potential.

e) Supporting resources: a package of additional supporting resources has also been developed by the BAD, British Dermatology Nursing Group and other stakeholders. These include an Isotretinoin Patient Guide, Acne Primary Care Referral Proforma, Acne Referral Guidance for Primary Care, Isotretinoin Side-effects Patient Questionnaire, and an Isotretinoin Follow-up Proforma. These supporting documents can be adapted to local needs and systems and are intended to be examples or templates to help support clinicians implement the new safety measures.

4. MHRA review of implementation of the recommendations

4.1 New research published after CHM IEWG report

To identify any additional evidence published since the last CHM review, the MHRA conducted independent literature searches covering January 2021 to December 2024. Searches were performed in PubMed, Embase, Web of Science, PsycINFO, and Scopus using the following two strategies:

1) Sexual dysfunction:

(isotretinoin OR Accutane OR Roaccutane OR 13-cis-retinoic acid OR retinoid) AND ('sexual dysfunction' OR 'erectile dysfunction' OR impotence OR libido OR gynaecomastia OR 'vulvovaginal dryness' OR anorgasmia OR orgasm difficulties OR hypoaesthesia OR 'vulva dryness' OR 'vulvovaginal dryness').

2) Neuropsychiatric disorders:

(isotretinoin OR Accutane OR Roaccutane OR 13-cis-retinoic acid OR retinoid) AND (psychiatric OR psychotic OR mood OR 'mental health' OR depression OR anxiety OR bipolar OR manic OR suicide OR suicidal OR 'self harm').

The BAD provided publications for review regarding the risks associated with isotretinoin, including two studies evaluating the risk of sexual dysfunction (Li et al., 2024; Tan et al., 2024a,) and four studies evaluating the risk of neuropsychiatric disorders (Kridin et al., 2022; Paljarvi et al., 2022; Rajput et al. 2024; Tan et al., 2024b).

The MHRA search identified no additional studies on sexual dysfunction beyond those reported by the BAD. For neuropsychiatric disorders, 16 studies were identified, including the four highlighted by the BAD. All were observational studies; no randomised controlled trials (RCTs) were found. The evidence base remains notably smaller for sexual dysfunction compared to neuropsychiatric risks.

Summaries of these studies are provided in Table 1 (excluding reviews and meta-analyses) in section 4.1.3 with further details in Annex A.

4.1.1 Publications on sexual function side effects

Tan et al. (2024a): This non-systematic scoping review considered 46 human studies, including five published from 2021 onwards. Of these, three addressed outcomes outside the scope of this review (menstrual irregularities, ovarian reserve, and semen parameters).

Li et al. (2024): This systematic review of 11 studies noted significant heterogeneity in study designs, precluding a meta-analysis. Most studies were case series with small sample sizes, lacking comparator groups, and affected by confounding, selection, and reporting biases. While evidence of a causal association between isotretinoin and sexual dysfunction was conflicting and based on studies of poor quality, the authors emphasized the importance of clinician and patient awareness of this uncertainty.

Overall, these reviews add little new evidence since the last CHM review.

4.1.2 Publications on mental health side effects

All the studies included patients aged under 18 years of age as summarised in Table 1, however, in each of the studies, results were only reported for all patients combined and not stratified by age groups.

4.1.2.1 Studies identified by the BAD

Kridrin et al. (2022): A retrospective cohort study using the TriNetX global federated health research network, comparing patients treated with isotretinoin with propensity score matched patients treated with oral antibiotics. The study found reduced risks of depression, post-traumatic stress disorder (PTSD), anxiety, bipolar disorder, schizophrenia, and adjustment disorder in the isotretinoin cohort. There was no evidence of an increased risk of major depressive disorder or suicide attempts, however, there was an increased risk of suicidal ideation. Key limitations included unclear population characteristics and whether outcomes were incident or pre-existing. A lower risk of all-cause mortality in the cohort treated with isotretinoin raises concerns about the comparability between groups.

Paljarvi et al. (2022): A retrospective cohort study (TriNetX network) comparing patients treated with isotretinoin with three groups of propensity score matched patients exposed to oral antibiotics, topical treatments, and no treatment. No evidence of increased neuropsychiatric risks was found. This robust study

controlled for acne severity but lacked information on the representativeness of the healthcare organisations contributing to TriNetX.

Rajput et al. (2024): A systematic review reporting reduced depression symptoms following isotretinoin treatment. There was no strong evidence of increased risks for newly diagnosed depression, other psychological conditions, or suicidal ideation in patients without pre-existing mental health conditions. However, patients with bipolar disorder experienced increased risks for mood disorders, including suicidal thoughts. The review presented no quantitative data and lacked methodological details.

Tan et al. (2024b): A systematic review and meta-analysis including 24 observational studies. The meta-analysis found no increased risk of psychiatric disorders, depression, anxiety, psychotic disorders, or sleep disorders at one year following treatment. Of the 24 studies, five were published from 2021 onwards (Chen et al., 2022; Kridin et al., 2023; Paljarvi et al., 2022); Ugonabo et al., 2021; Vona-Girault et al., 2023) which are discussed individually.

4.1.2.2 Additional studies identified by the MHRA

AlGhofaili et al. (2021): A prospective cohort study (179 patients, Saudi Arabia) comparing patients treated with isotretinoin with those treated with topical retinoids. No evidence of an increase in depression scores was observed from baseline to three-, or six-months. Limitations included a small size and potential selection, channelling, and response biases.

Chen et al. (2022): A retrospective cohort study (29,943 patients, Taiwan (PRC)) comparing patients treated with isotretinoin with an unexposed cohort. No evidence of an increased risk of any of the psychiatric disorders was observed (all disorders, anxiety, Obsessive Compulsive Disorder (OCD), manic disorder, major depressive disorder, bipolar disorder, schizophrenia, suicidality). There was a lack of clarity on what, if any, treatments the comparator group were exposed to, and limitations including the potential for channelling bias.

Droitcourt et al. (2024): A case-time-control study (2,284 patients, France) evaluating whether patients have an increased risk of an acute-onset psychiatric event within two months of isotretinoin initiation, compared to two-to-four months after initiation. The study did not find evidence of an increased risk. Generalisability was limited due to the outcome definition being restricted to hospitalisations of eight hours or more, and all patients having been exposed to isotretinoin.

Hekmatjah et al. (2021): A cross-sectional survey (>9 million patients, applying person-level sampling weights, USA) comparing patients treated with isotretinoin

with those treated with oral antibiotics. Lower levels of depression symptoms were reported in patients treated with isotretinoin. However, it was not possible to determine the temporal association between exposure and outcome, and the study was subject to channelling bias.

Öğüt et al. (2023) and Orenary et al. (2024): Two small self-controlled studies (17 and 42 patients, Turkey) comparing depression and anxiety symptoms at baseline and at three-months of follow-up after initiating isotretinoin treatment. Neither found evidence of an increase in depression or anxiety symptoms, but both were limited by small sample sizes and lack of comparator groups. In addition, the Öğüt study had a high drop-out rate (43%).

Ugonabo et al. (2021): A retrospective cohort study (72,555 patients, USA) comparing patients treated with isotretinoin with those treated with oral antibiotics. Evidence of a decreased risk of mood disorders and psychiatric disorders requiring medication was reported. There was no evidence of an association with anxiety disorder or suicidal behaviour. However, an increased risk of mania and psychotic disorder was reported. Outcomes were based on prevalent psychiatric diagnoses so may have been pre-existing prior to drug exposure.

Vona-Giralt et al. (2022): A self-controlled study (4,738 patients, Spain) compared the occurrence of new psychiatric diagnoses during isotretinoin exposure and pre/post exposure. No evidence of increased risks was identified. However, the study population was limited to women of child-bearing potential age, and the choice of study design was not appropriate for non-acute outcomes.

The MHRA literature review identified four additional literature and systematic reviews (Bremner et al., 2021; Chanrasekaran et al., 2021; Deluca et al., 2021; Fernandes et al., 2023). All studies published from 2021 onwards were included in the reviews have been discussed above.

4.1.3 Discussion

The evidence base is characterised by heterogeneity in study populations, sample sizes, comparison groups, and outcomes. Many of the studies were limited by small sample sizes, unclear definitions of incident outcomes vs. pre-existing conditions, lack of information on dose, duration, and prior treatments, and potential biases, including confounding by indication, selection and channelling bias. While none of the newly published studies provide strong evidence supporting a causal association between isotretinoin and increased risks of neuropsychiatric outcomes, methodological shortcomings and conflicting findings limit their validity.

Table 1. Observational studies published from 2021 onwards evaluating the risk of neuropsychiatric events (n = 10) (excluding systematic and literature reviews)

Study	Study design /Comparator	Sample size/Patient age/Country	Potential confounders /Adjustment	Results (fully adjusted if available)	Authors' conclusion for isotretinoin	Assessor's comments
AlGhofaili, 2021	Prospective cohort Isotretinoin vs. topical retinoids	179 patients Mean age: 21.35 (SD: 2.96) years Saudi Arabia	None	ANOVA p-value comparing changes in depression scores from baseline to 3 and 6 months: 0.885	No evidence of an increased risk	Several limitations including potential selection, channelling and response bias.
Chen, 2022	Retrospective cohort Isotretinoin exposed vs. unexposed	29,943 patients Mean age 38.00 (SD: 20.27) years (No patients under 20 years) Taiwan (PRC)	Sex, age, CCI	Overall psychiatric disorders: HR: 1.009 (0.422 - 1.696) Anxiety: HR: 1.022 (0.428 - 1.711) Obsessive-compulsive disorder: HR: 1.201 (0.503 - 2.007) Manic disorder: HR: 1.014 (0.422 - 1.709) Major depressive disorder: HR: 0.953 (0.398 - 1.613) Bipolar disorder: HR: 1.053 (0.433 - 1.787) Schizophrenia: HR: 1.000 (0.418 - 1.692) Suicidality: HR: 0.982 (0.398 - 1.622)	No evidence of an increased risk	Several limitations including lack of clarity on what, if any, alternative acne treatments the comparator group were exposed to, and the potential for channelling bias.
Droitcourt, 2024	Case-time-control in cohort of isotretinoin initiators 4-2 months prior vs. 2-0 months prior	262,786 patients Mean age: 18.4 (SD 3.0) years France	Matched on sex, age, and index date	Severe acute-onset psychiatric event: OR: 1.01 (0.72 - 1.41)	No evidence of an increased risk	Limited to severe acute-onset psychiatric events requiring a hospital stay of more than 8 hours – cannot be generalised to psychiatric disorders managed in primary care. Not possible to assess risks compared with a non-isotretinoin group.
Hekmatjah, 2021	Cross-sectional Isotretinoin vs. oral antibiotics	9,046,894 patients (applying person-level sampling weights)	Age, gender, race, ethnicity, employment status, region, education level, insurance coverage,	Depressive symptoms score: β: -0.337 (-0.503 - -0.171) Psychological distress score: β: -0.759 (-1.493 - -0.043)	Evidence of an association between isotretinoin exposure and	Several limitations including cross-sectional nature (unable to determine temporal association) and potential channelling bias.

		Mean age: 33.2 (SD:0.61) years USA	poverty level category, social limitations, cognitive limitations, CCI		fewer depressive symptoms / less psychological distress	
Kridin, 2022*	Retrospective cohort Isotretinoin vs. oral antibiotics	151,416 patients Mean age: 21.7 (SD: 9.1) years International (29% Hispanic or Latino)	Propensity score matched for age, sex, race, ethnicity, smoking, obesity, diabetes mellitus, hypertension, hyperlipidaemia, ischemic heart disease, chronic kidney disease, problems related to education and literacy, problems related to employment and unemployment, occupational exposure to risk factors	Depression: HR: 0.90 (0.87 - 0.93) Major depressive disorder: HR: 0.97 (0.92 - 1.03) Suicidal attempts: HR: 0.97 (0.85 - 1.11) Suicidal ideation: HR: 1.14 (1.32 - 1.50) Post-traumatic stress disorder: HR: 0.75 (0.68 - 0.82) Anxiety: HR: 0.84 (0.82 - 0.87) Bipolar disorder: HR: 0.65 (0.59 - 0.72) Schizophrenia: HR: 0.60 (0.48 - 0.76) Adjustment disorder: HR: 0.82 (0.77 - 0.87)	Evidence of a decreased risk of depression, post-traumatic stress disorder, anxiety, bipolar disorder, schizophrenia, and adjustment disorder. No evidence of an increased risk of major depressive disorder or suicide attempts. Evidence of an increased risk of suicidal ideation.	Several limitations including lack of clarity of population characteristics, and whether outcomes were incident (newly diagnosed following exposure) or prevalent (pre-existing). It is notable that the risk of all-cause mortality was significantly lower among those treated with isotretinoin, raising concerns about comparability between the isotretinoin and oral antibiotic groups.
Öğüt, 2023	Self-controlled cohort of isotretinoin initiators Baseline vs. 3-months	17 patients Mean age: 20.4 (SD: 2.1) years Turkey	Self-controlled	Depression symptoms score: t: 3.04, p-value: 0.008 Anxiety symptoms score: t: 2.72, p-value: 0.015	Evidence of a reduction in depression and anxiety symptoms following initiation	Several limitations including high drop-out rate (43%) and lack of comparator group
Orenay, 2024	Self-controlled cohort of isotretinoin initiators Baseline vs. 12-weeks	42 patients Mean age: 20.47 (SD:4.01) years Turkey	Self-controlled	Depressive symptoms score: p-value: 0.53	No evidence of a change in depression symptom scores following initiation	Several limitations including lack of comparator group

Paljarvi, 2022*	Retrospective cohort study Isotretinoin vs. oral antibiotics, topical medicines, and no treatment	262,647 patients Age range 12-27 years International (91% USA)	Propensity score matched for type of acne, comorbidities, and history of mental health problems	*Outcome:* *Compared to oral antibiotics* *Compared to topical medications* *Compared to no treatment* Any neuropsychiatric outcome: OR: 0.80 (0.74 - 0.87) OR: 0.94 (0.87 - 1.02) OR: 0.80 (0.74 - 0.87) Psychotic disorders: OR: 1.09 (0.61 - 1.98) OR: 1.00 (0.56 - 1.78) OR: 1.12 (0.66 - 2.22) Mood disorders: OR: 0.78 (0.71 - 0.87) OR: 0.95 (0.85 - 1.06) OR: 1.13 (1.00 - 1.27) Anxiety disorders: OR: 0.79 (0.72 - 0.87) OR: 0.91 (0.83 - 1.00) OR: 1.13 (1.02 - 1.25) Personality disorders: OR: 0.74 (0.53 - 1.04) OR: 0.75 (0.54 - 1.05) OR: 0.87 (0.60 - 1.26) Behavioural disorders: OR: 0.82 (0.70 - 0.97) OR: 0.88 (0.75 - 1.04) OR: 0.92 (0.78 - 1.09) Sleep disorders: OR: 0.90 (0.77 - 1.04) OR: 1.10 (0.95 - 1.28) OR: 1.19 (1.10 - 1.40) Self-harm, nonfatal: OR: 0.85 (0.66 - 1.11) OR: 1.22 (0.93 - 1.59)	No evidence of an increased risk	A large and well conducted observational study. Primary limitation is lack of information on whether the healthcare organisations included are representative of the patient population.

				OR: 1.25 (0.93 - 1.68)		
Ugonabo, 2021	Retrospective cohort study Isotretinoin vs. Oral antibiotics	72,555 patients Age range 12-35 years USA	Age, sex, length of time enrolled in the claims database	All psychiatric disorders: OR: 0.88 (0.85 - 0.91) Mood disorder: OR: 0.90 (0.85 - 0.94) Anxiety disorder: OR: 0.96 (0.92 - 1.01) Mania or psychotic disorder: OR: 1.15 (1.01 - 1.32) Other mental disorders: OR: 0.93 (0.88 - 0.97) Psychiatric disorder requiring medication: OR: 0.83 (0.80 - 0.87) Suicidal behaviour: OR: 1.00 (0.83 - 1.21)	Evidence of a decreased risk of mood disorders, or psychiatric disorders requiring medication. No evidence of an increased risk of anxiety disorder, or suicidal behaviour. Evidence of an increased risk of mania or psychotic disorder.	Several limitations include outcomes being based on prevalence of psychiatric diagnoses (so may have been pre-existing).
Vona-Giralt, 2022	Self-controlled cohort of isotretinoin users Exposure period vs. pre-exposure period, and exposure period vs. post-exposure period	4,738 patients Mean age 23.2 (SD: 10.9) years Spain	Self-controlled	Incident psychiatric events: *Compared to pre-exposure* IRR: 1.12 (0.92 - 1.36) *Compared to post-exposure* IRR: 0.87 (0.72 - 1.07)	No evidence of an increased risk	Several limitations include the study population being restricted to women of child-bearing potential age and using a self-controlled approach to assess non-acute outcomes.

95% confidence intervals are presented in brackets where available. ADHD: Attention-deficit/hyperactivity disorder; CCI: Charlson Comorbidity Index; HR: Hazard ratio; OR = Odds ratio; t = Student's t-test. *Indicates studies submitted to the MHRA by the BAD. All other studies identified by the MHRA via an independent literature review.

4.2 Immediate post implementation issues

4.2.1 Post implementation (November 2023 - March 2024)

Prior to implementation of the new regulatory measures, it was acknowledged that there was wide variation in clinical practice throughout the country. However, feedback received from stakeholders, after implementation, suggested that there was even greater variation than first thought. In particular, with regards to the set-up of dermatology clinical services, in clinical practice (reviewing patients over telephone) including prescribing practice (e.g. FP10 prescriptions for isotretinoin for the entire treatment course, given to the patient at the initial assessment by the Lead Prescriber), and the types of healthcare professional that staff these services (e.g. dermatology acne clinics solely run by one Band 7 nurse).

Feedback from the BAD and other stakeholders indicated the absence of Band 7 nurses was causing disruption to clinics especially those principally led by Band 7 nurses. In light of this, in January 2024 CHM was asked to review the list of healthcare professionals considered to be appropriately qualified to be a Lead Prescriber. CHM advised the inclusion of Band 7 Dermatology Clinical Nurse Specialists as suitable Lead Prescribers in January 2024, to support trusts in implementing the new regulatory requirements for isotretinoin.

4.3 Impact monitoring strategy

In March 2024, the advice of the Pharmacovigilance Expert Advisory Group (PEAG) was sought on a provisional strategy for potential ways to monitor the impact of the new regulatory measures introduced in October 2023. The strategy discussed several process and outcome indicators and the feasibility and requirements of measuring them.

Process indicators would require obtaining data from various sources, however the detailed coding of records is not available to allow this type of analysis.

Outcome indicator 1. Neuropsychiatric and sexual adverse events reported through Yellow Cards

Outcome indicator 2. Adverse events reported through social media was not recommended

Outcome indicator 3. Drug utilisation and incidence of adverse events using Observational Health Data Sciences and Informatics (OHDSI) partner data, Secondary care prescribing data and Private prescribing data.

Outcome indicator 4. Marketing Authorisation Holder (MAH) led Post Authorisation Safety Study (PASS).

4.3.1 Progress

Outcome indicator 1. The MHRA continues with its routine pharmacovigilance activities including analysing Yellow Card reports for signals related to exposure in pregnancy, mental health and sexual function and other possible adverse drug reactions. No trends have been observed in the Yellow Card reporting relating to mental health, sexual function and pregnancy (see summary in Table 2 and full data in Annex B) other than the overall number of reports of mental health side effects associated with isotretinoin, which have been reducing.

In addition, a project is being undertaken with the University of Liverpool to look at the number of pregnancies associated with the use of isotretinoin pre, during and post COVID. Due to missing secondary care data on isotretinoin prescription this will be challenging, however, more data could become available.

Table 2. Summary of Yellow Card reports

Year	Psychiatric disorders	Reproductive system and breast disorders	Pregnancy
2019	60	28	1
2020	68	19	1
2021	53	20	1
2022	46	28	2
2023	38	29	4
2024 to Aug 24	38	28	1

Outcome indicator 3. The NIHR-funded ACNE-ID study is underway to compare the risks and benefits of two different doses of isotretinoin for the treatment of severe acne in young people aged 12-24 years.

The Model Health System is a data-driven improvement tool that supports health and care systems to improve patient outcomes and population health. It provides benchmarked insights across the quality of care, productivity and organisational culture to identify opportunities for improvement. Access to the Model Health System was obtained and there was data on isotretinoin expenditure and volume prescribed relative to activity. An illustrative example is shown in Figure 1 and 2 for an organisation whose value is compared with a peer median and a national median, which are generally informed by top deciles for 2019. It showed downward system trends over a 4-year period. It is unclear why this particular organisation was different from peers; it could be related to how the clinical pathways are designed. However, it is important to note that the data set ends Q3 2023/24 which was

when the isotretinoin implementation report was published (October 23) with a 6-month transition.

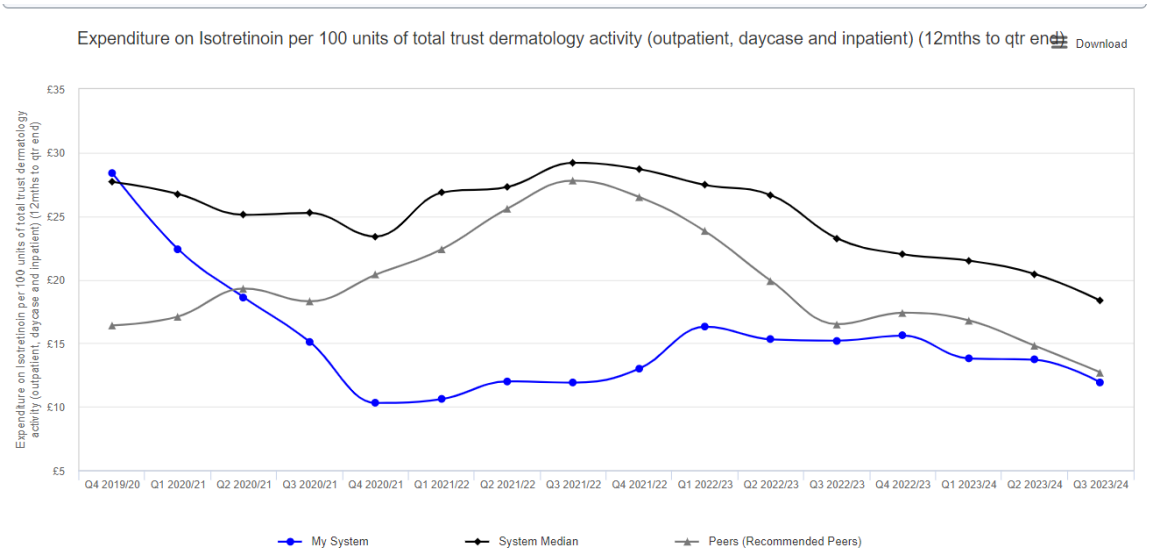


Figure 1. Example of expenditure on isotretinoin per 100 units of activity at an ICB

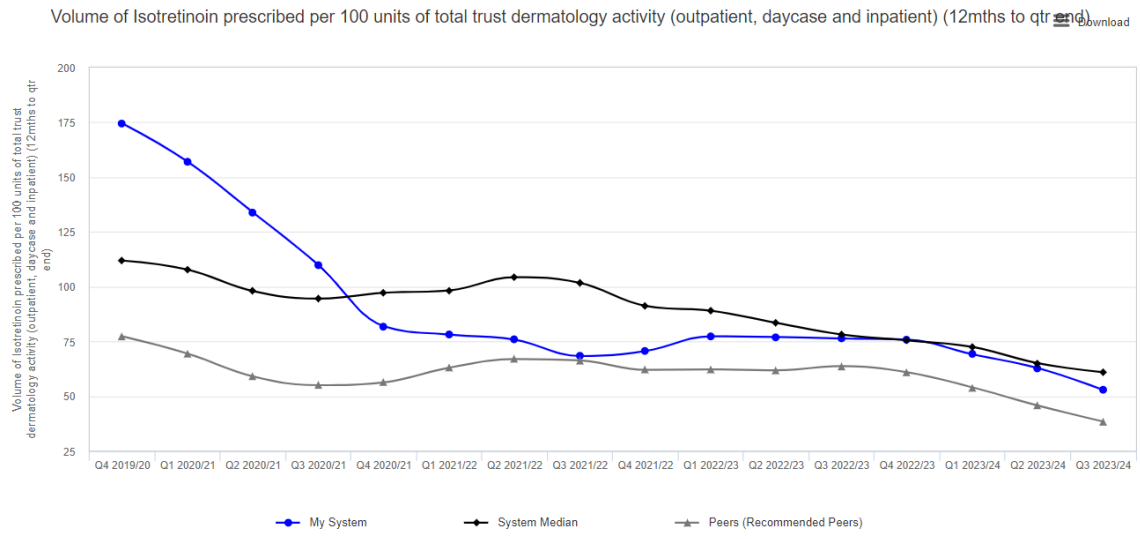


Figure 2. Example of volume of Isotretinoin prescribed per 100 units of activity at an ICB

The private Independent Healthcare Providers Network (IHPN), formerly known as the NHS Partners Network, was also contacted by the MHRA, but they do not hold any data sources.

Outcome indicator 4. This relates to a MAH led PASS, which is progressing with the protocol submitted by the consortium of MAHs. The protocol has been assessed and advice received from PEAG and CHM which has been shared with the MAH consortium to revise the protocol accordingly.

4.3.2 Trends in dermatology referral rates and estimated waiting times

In order to determine if the new regulations had impacted referrals and waiting times an analysis looking for trends in Clinical Practice Research Datalink (CPRD) data was performed.

4.3.2.1 The Clinical Practice Research Datalink (CPRD)

The CPRD comprises anonymised patient electronic healthcare record (EHR) data collected routinely in primary care. The data includes a full historic record of the coded part of the practice's electronic health records including data on deceased patients and those who have left the practice. Anonymised data collected within the CPRD Aurum primary care database includes patient demographics, diagnoses, symptoms, prescriptions, referrals, immunisations, lifestyle factors, tests and results. Aurum does not capture medicines prescribed in secondary care settings but will capture subsequent prescription where prescribing responsibility reverted to GPs. As of September 2024, the database includes approximately 49.5 million patients, of which 16.5 million patients are in active follow-up (representing 24.7% of the UK population and 20.1% of UK general practices). These data were extracted following approval of a feasibility study protocol.

4.3.2.1.1 Rationale for the study

Isotretinoin is a drug used to treat severe forms of acne where other treatments have proved unsuccessful. Isotretinoin is predominantly prescribed by specialist dermatologists in secondary care settings; however, a small proportion of prescribing does occur in primary care by General Practitioners with an extended role (GPwER). Given the lack of available data for research which captures prescribing in secondary care, the CPRD was used to evaluate the unintended consequences in primary care of the recently updated risk minimisation measures on all-cause referrals to dermatology and estimated waiting times between referral and patients receiving a first oral isotretinoin prescription. It is assumed that the data presented in these analyses occurred where isotretinoin prescriptions were issued by GPwERs, but it is not possible to confirm this. It is also not possible to infer the reason for the referral within the CPRD database, hence these analyses are based on all-causes.

Analysis 1. Trends in dermatology referral rates

Aim

To describe trends in all-cause dermatology referral rates stratified by age groups (<18 years and 18 years and above). (Note it is not possible to determine the reason for the referral in CPRD).

Methods

Data on patients with a dermatology referral code (not specific to acne, see Table 3) were extracted from CPRD Aurum using the September 2024 database build.

The numerator comprised patients with a dermatology referral code in a calendar quarter (patients with more than one referral code in a quarter were counted once). The denominator comprised all patients of the respective age-group in active follow-up for the entirety of that quarter. Patient follow-up commenced at the current registration date and was censored at the earliest of the last data collection date, registration end date or date of death.

Results

Figure 3 shows the all-cause dermatology referral rates exhibit seasonal fluctuation. The dermatology referral rates tend to be higher in the older age-group rather than younger age-group. For both age-groups, referral rates tended to show an overall increase between Q1 2015 and Q1 2020 and declined rapidly in Q2 2020 due to COVID-19 lockdown restrictions before increasing again thereafter. In the under 18 years age-group referrals increased from 186 per 100,000 patients in Q1 2015 to 222 per 100,000 in Q1 2020 before falling to 93 per 100,000 in Q2 2020. In Q3 2020 the referral rate increased to 182 per 100,000 and increased again reaching 281 per 100,000 in Q1 2024.

In the 18 years+ age-group, the referral rate was 439 per 100,000 in Q1 2015 and increased to 402 per 100,000 in Q1 2020 and then fell to 162 per 100,000 in Q2 2020. The rate then increased to 353 referrals per 100,000 in Q3 2020 and increased further to 452 per 100,000 in Q1 2024. This could be related to a post-Covid 19 catch-up.

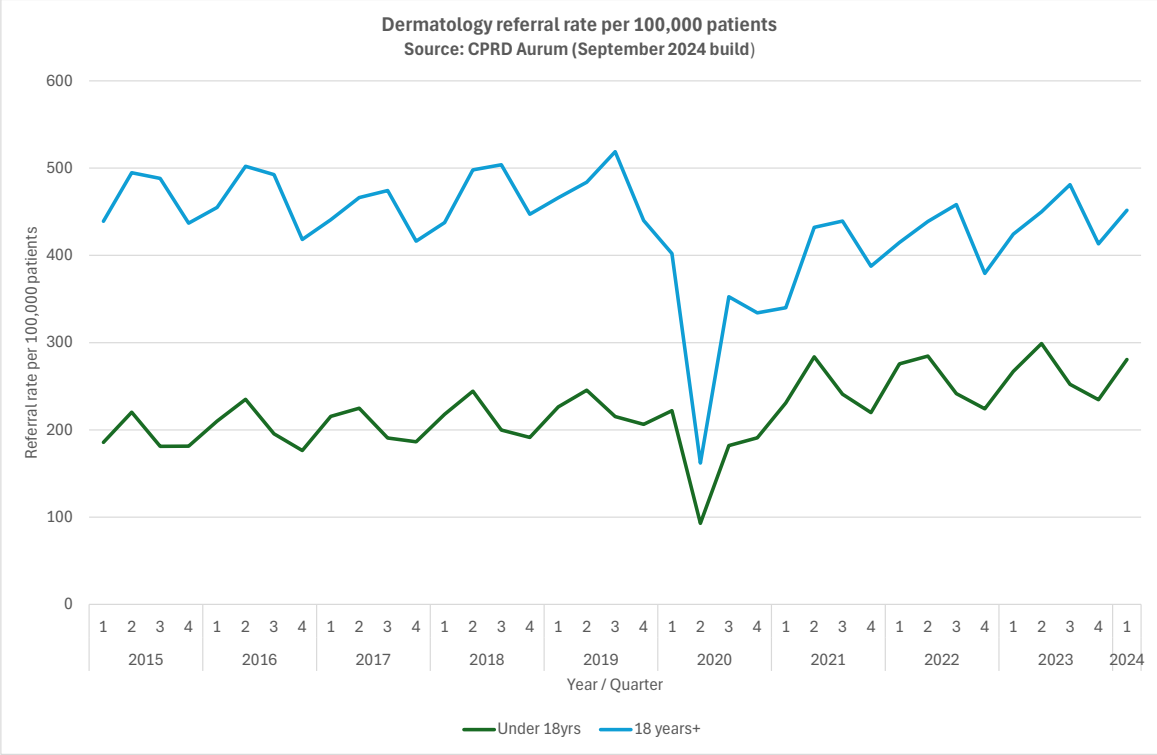


Figure 3. Trends in dermatology referral rates as recorded in CPRD Aurum

Analysis 2. Dermatology referral waiting times

Aim

To evaluate patterns in waiting times between a dermatology referral and a first oral isotretinoin prescription.

Methods

Data on patients with a first prescription for isotretinoin (index date) issued between 1st January 2015 – 31st March 2024 and a dermatology referral medical code recorded prior to the index date were extracted using the medical codes in table 3. If a patient had more than one dermatology referral code, then the code which was closest but prior to the index date was retained. The waiting time was defined as the time in weeks between the date of the dermatology referral code and the index date. Patients had to be in active follow-up, which commenced at the current registration date (there is no up-to-standard date currently in Aurum) and was censored at the earliest of the last data collection date, registration end date or date of death. It was not possible to further stratify these data according to age-groups due to CPRD requirements on reporting data with small numbers of events.

Results

The results suggest that waiting times have increased over time (figure 4), particularly for patients exceeding the 18-week target. In 2015, the proportion of patients waiting more than 18 weeks was approximately 42% and has increased to approximately 78% in 2023 (note that the new regulations were introduced on 31 October 2023). It is therefore clear that waiting times had already increased substantially prior to the introduction of the new regulatory measures. The results for 2024 are based on only one quarter's worth of data and so are incomplete, although they indicate the waiting times similar to 2023.

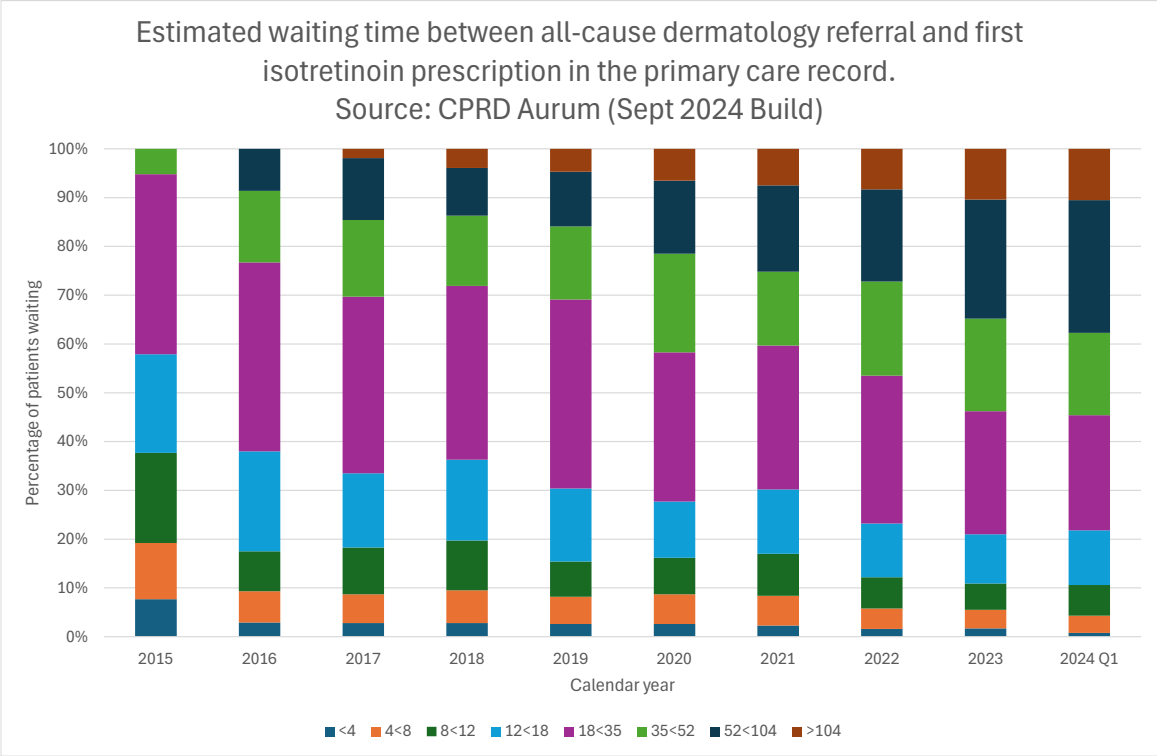


Figure 4. Estimated waiting times between referral and a first isotretinoin prescription (CPRD Aurum) (Year refers to the year the first isotretinoin prescription was issued, i.e. index date). The columns represent the proportion of patients in each waiting time category measured in weeks between an all-cause dermatology referral and a first isotretinoin prescription as recorded in the primary care record (CPRD does not capture prescriptions issued in secondary care). Note the numbers of patients waiting >104 weeks are likely to include implausible waiting times and should be interpreted with caution but have been included here for transparency given national NHS waiting time statistics show some patients are waiting such times. Note that 2024 is based on incomplete data and only based on prescriptions issued up to 31st March 2024.

Data from the BAD received 31 January 2025

GIRFT (Get it right first time) Data was received from the BAD showing long wait data for under 18s as shown in figure 5.

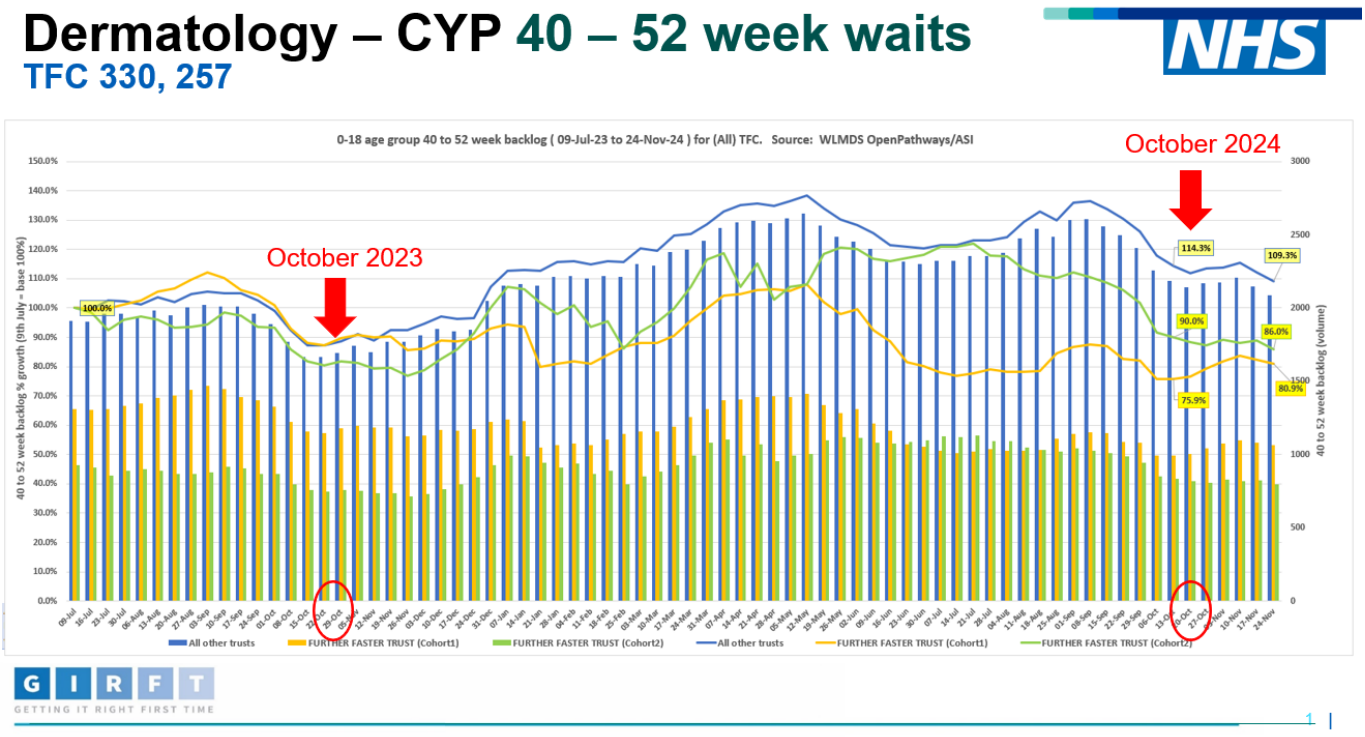


Figure 5. Data from the BAD showing wait date for under 18s. Legend: Blue – All other Trusts, Yellow – Further Faster Trust (cohort 1), Green – Further Faster Trust (cohort 2)

Discussion

The referral data were compared with the NHS e-Referral Service (e-RS) dashboard (https://digital.nhs.uk/dashboards/ers-open-data), which displays anonymised referral data across England and includes more up-to-date near real-time data but cannot be stratified by age-group. The e-RS data show that all-cause dermatology referrals have increased again throughout 2024 with a rolling average of 20,000 referrals per week but appear to be at their highest level since 2020 when they averaged 12,000 per week.

The e-RS is understood to be a standalone system which is not integrated with the GP practice clinical software and so when a GP submits a referral request through e-RS, the referral request will not automatically appear in the patient EHR. The GP will have to manually code the referral in the patient record. What code is used could vary widely and whilst these analyses used dermatology-specific codes, some GPs may use non-specific generic referral codes. Some GPs may not record the referral at all, and the speciality input may have only been captured on receipt of the letter back from the speciality. Whilst the CPRD analyses could be repeated to include generic referral codes, it would be very difficult, if not impossible, to attribute these referrals to acne and isotretinoin treatment and could be due to other unrelated health conditions.

The e-RS system does not include information for patients that have had a referral, booking or attempted booking outside of the e-RS which may also explain differences in trends between the e-RS and CPRD Aurum. It is important to note that the e-RS is anonymised and does not include information on patient demographics such as age, sex or clinical diagnosis.

The CPRD analyses are consistent with nationally available NHS waiting time statistics (https://www.england.nhs.uk/statistics/statistical-work-areas/rtt-waiting-times/), which shows that the proportion of patients waiting longer than the 18 week target has increased.

As isotretinoin is predominantly prescribed in secondary care, the data presented here are based on a smaller sample of prescriptions issued in primary care and so the waiting times may not be generalisable to the wider isotretinoin-treated population in secondary care. Possible reasons for isotretinoin prescriptions of issued in primary care include prescribing by GPwER in dermatology (approximate figure of accredited dermatology GPwER from the Primary Care Dermatology Society is 50-100), outsourced providers of dermatology services who use the community prescribing systems e.g. DMC healthcare, prescription following independent private consultation.)

With regard to Figure 5, the IIAEWG report was published on 31 October 2023, and the new regulations would not have been implemented immediately as they required changes to services (May 2024 was the guidance timeframe given by the BAD for implementation). In addition, many trusts stopped services for several months in order to reconfigure services which would have impacted waiting times. There was also a dip in waiting times prior to October 2023, although the reasons for this are unclear. It is very challenging therefore to be able to isolate the impact of solely the second prescriber regulation from this data.

Conclusion

Dermatology referral rates appeared to be consistently high prior to the COVID-19 pandemic and fell at the start of the pandemic during Q2 2020 but have increased again since then (Figure 3). However, waiting times between a dermatology referral and a first isotretinoin prescription have been on an increasing trajectory since 2015 (when the IIAEWG recommendations were not in place), with increasing proportions of patients exceeding the 18-week target. There is no clear evidence from this data of an increase in time between first referral and prescription of isotretinoin in 2024 (noting that only data from Q1 is available). Although rates have not decreased, they are comparable to 2023 when the regulatory measures were not in place, noting waiting lists were increasing prior to the new regulatory measures. Without the use of a suitable comparator discipline, it is difficult to determine if waiting lists are increasing due to the regulatory changes alone.

Table 3. Codelist used to identify dermatology referrals

medcodeid	term	snomedctconceptid
1120171000000114	Referral to dermatology clinical assessment service	504181000000101
1561621000006116	Referral to dermatology special interest general practitioner	248991000000109
1757131000000116	Referral to community dermatology service	785701000000106

1775031000006117	Teledermatology referral	1775031000006101
1775081000006116	Referral to community dermatology service	1775081000006100
1775371000006116	Referred to Dermatology Service	1775371000006100
1851001000006111	Internal practice dermatology referral	1851001000006107
2171371000000116	Referral to teledermatology service	836201000000101
2297371000000119	Internal practice dermatology referral	892161000000103
2533379011	Referral to dermatology nurse specialist	415268007
2548477010	Referral to paediatric dermatology service	416076006
283598012	Dermatological referral	183518005
284110017	Private referral to dermatologist	183897008
451825013	Referral to dermatologist	308472003
4724201000006112	Referral to dermatology service	183518005
5948091000006117	Referral by dermatologist	305966007
6890051000006114	Referral to paediatric service for acne	416291002
904841000006116	Dermatology referral	904841000006100

4.3.3 Prescribing trends of isotretinoin, lymecycline and doxycycline

Usage data was analysed to evaluate trends in the prescribing of isotretinoin and the oral antibiotics tetracycline, lymecycline (408mg) and doxycycline which are alternative acne treatments.

The usage data was derived from the IQVIA MIDAS database, which captures the volume of drug dispensed by prescription in UK retail and hospital pharmacies. Retail dispensing data is based on volumes of products dispensed against a prescription in retail pharmacies and wholesaler sell-in data to dispensing doctors (a proxy for dispensed product). Hospital dispensing data covers usage/consumption levels of medicinal products within NHS hospitals (irrespective of their source of supply). These data have already been projected to UK wide figures within MIDAS.

The database may include drugs which are either prescription-only-medicine (POM) or able to be prescribed but also may be obtained over-the-counter (OTC) (e.g. ibuprofen). The database does not include data on such products that may be obtained via OTC sales or products that may be obtained from sources other than NHS hospital pharmacies or retail pharmacies e.g. supermarkets, military or private hospitals.

This data is not patient-level therefore, it is not possible to attribute any changes in usage over time to a specific indication or to stratify according to patient characteristics. The data also only captures the previous 5 years dispensing, so there is no data available prior to October 2019. Usage within MIDAS is expressed as units (number of packs) dispensed.

Methods

Data were extracted from IQVIA MIDAS for the time period October 2019 to September 2024, and data is presented in 12-month time intervals. Data on sector (Hospital/Retail), product name, pack size, New Form Code (NFC123), chemical salt, was extracted.

There were defined daily doses (DDDs) recorded for the dose form and indication on the WHO ATC DDD website [ATCDDD - ATC/DDD Index]. However, assigning DDDs was complex due to the variation in dosage which is dependent on the age and weight of the patient in addition to the indication of use according to the BNF prescribing information[4]. As a result, the usage measure presented was the number of packs.

Results

Oral isotretinoin

The overall use of oral isotretinoin by sector is shown in Figure 6. The graph compares usage between the hospital and retail sectors across the 5-year period in terms of the number of packs dispensed. Usage was higher in the hospital sector compared to the retail sector in the Moving Annual Total (MAT) Q3 2020 (i.e. covers the period 2019 Q4 to 2020 Q3) and in MAT Q3 2023. In the remaining MATs (Q3 2021, 2022, 2024), the retail sector showed a higher volume of usage than that seen in the hospital sector. There has been a drop in hospital usage within this data set. This could be related to possible increased use by primary care, private contractors commissioned by the NHS and use NHS prescriptions, or due to the regulatory measures.

[4] BNF Prescribing information: Isotretinoin < https://bnf.nice.org.uk/drugs/isotretinoin/>; Lymecycline < https://bnf.nice.org.uk/drugs/lymecycline/ > ; Doxycycline < https://bnf.nice.org.uk/drugs/doxycycline/ >

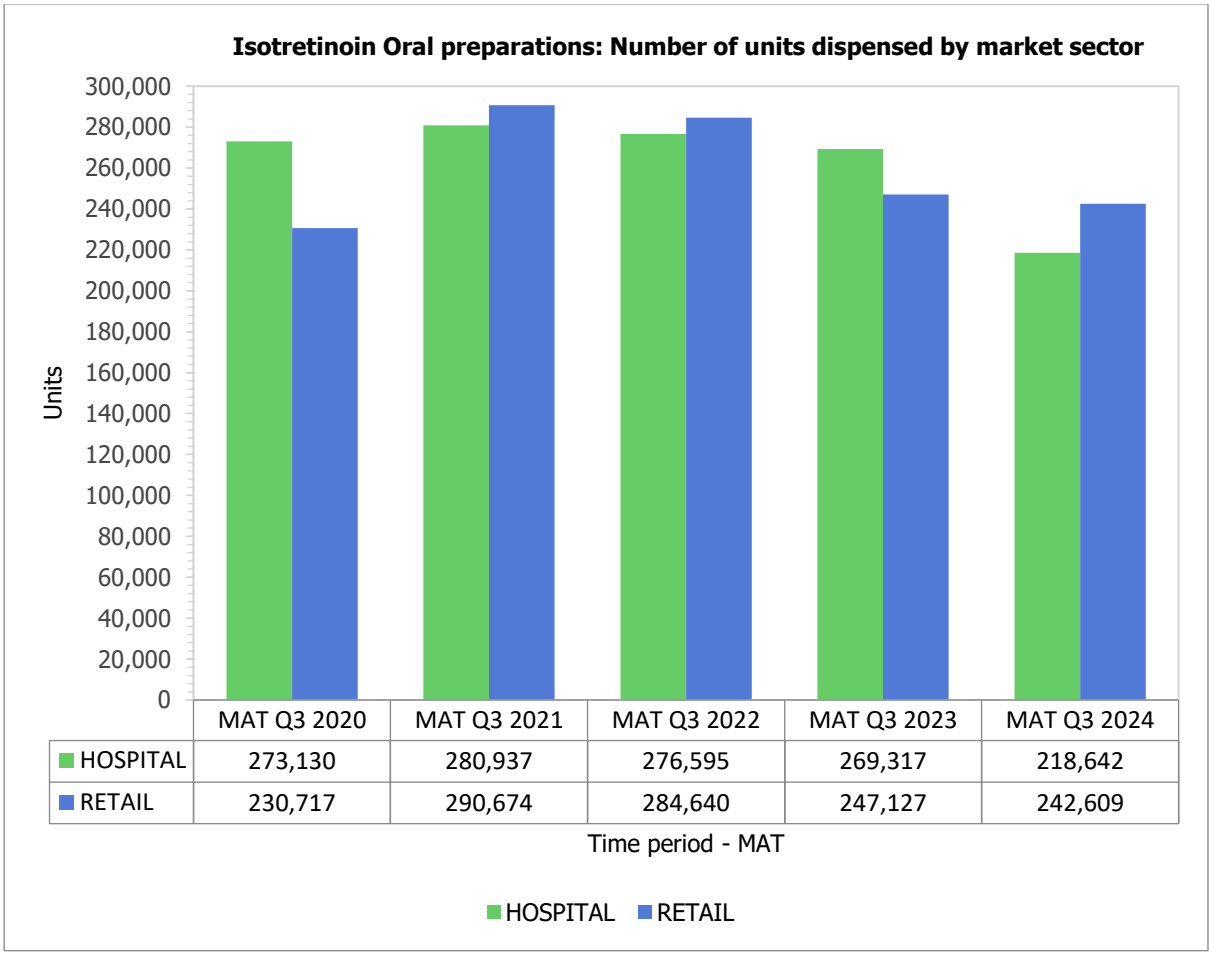


Figure 6. Usage of Oral Isotretinoin by sector, hospital and retail, based on number of packs dispensed.

Oral lymecycline

The overall use of oral lymecycline by sector is shown in Figure 7. The graph shows greater usage in the retail sector compared to the hospital sector across the 5-year period. At least 98% of oral lymecycline usage was in the retail sector and has remained relatively consistent over time.

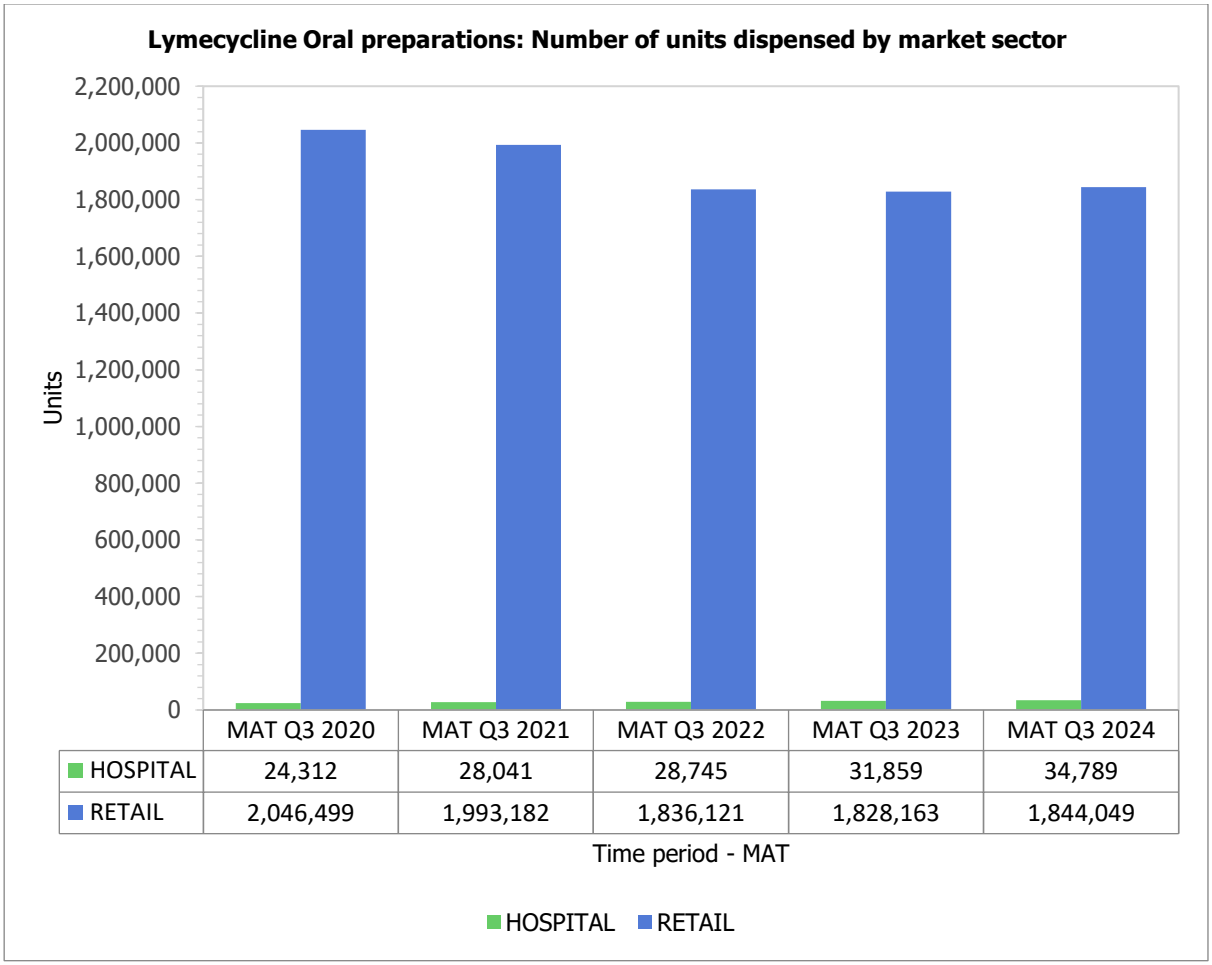


Figure 7. Usage of Oral Lymecycline by sector, hospital and retail, based on number of packs dispensed.

Oral doxycycline

The overall use of oral doxycycline by sector is shown in Figure 8, and illustrates that the majority of oral doxycycline usage was in the retail sector compared to the hospital sector across the 5-year period. At least 87.7% of oral doxycycline usage was in the retail sector. The data shows a drop in usage in the time frame MAT Q3 2021 but usage in the following MAT period returned to similar levels as the previous year. This could possibly be a result of the pandemic; however, this trend was not seen with oral lymecycline usage.

Approximately 97% of all doxycycline packs dispensed were for the 100mg strength tablets.

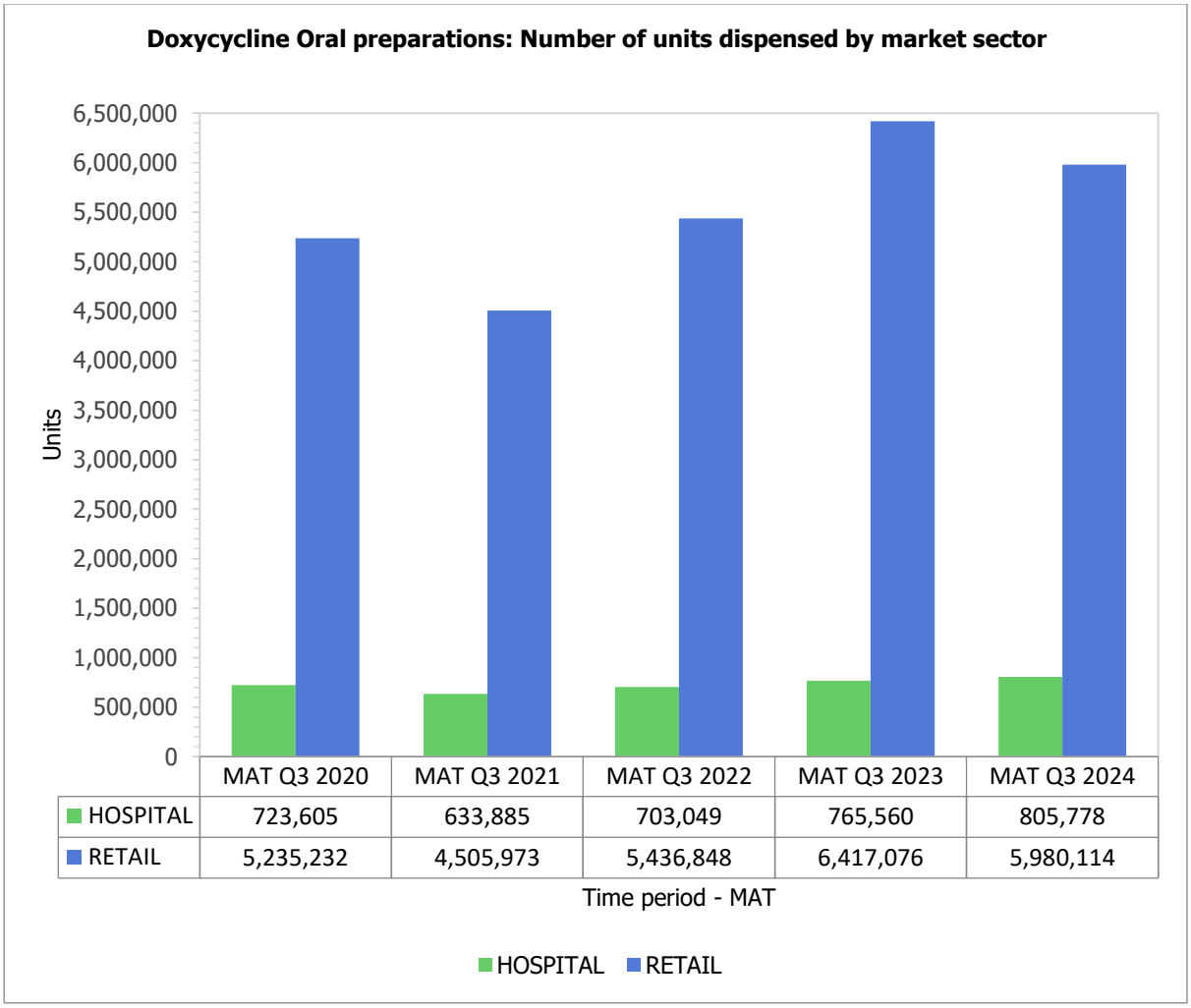


Figure 8. Usage of Oral Doxycycline (all strengths) by sector, hospital and retail, based on number of packs dispensed.

Discussion

Another channel of access to isotretinoin would be via private prescribing. Whilst private prescriptions could be dispensed in both NHS hospital pharmacies and community (retail) pharmacy, acceptance of private prescriptions at NHS hospital pharmacies is dependent on the local policy as determined by the associated hospital trust.

Private prescriptions for isotretinoin can be issued via private dermatology clinics or private GP services. It is unclear if these outlets have dispensing services. IQVIA MIDAS would not capture private prescription dispensing from these outlets. The exception is when the patient takes their private prescription to their local community pharmacy for dispensing. These would be captured under the retail sector (sell-out dataset) within MIDAS.

In summary, IQVIA MIDAS data would capture private prescriptions submitted to and dispensed by NHS hospital pharmacies and community (retail) pharmacies. The data set, however, would not capture the private prescriptions submitted for dispensing via other outlets.

Similar to other dispensing and prescribing data sets, a dispensed product does not indicate the patient had taken the product and it is not possible to measure treatment compliance.

4.3.4 Trends in isotretinoin use in secondary care

The Secondary Care Medicines Data (SCMD), hosted by NHS Business Services Authority (NHSBSA) on behalf of NHS England (NHSE), contains processed pharmacy stock control data in the Dictionary of Medicines and Devices (dm+d) standardised Virtual Medicinal Product (VMP) format from all NHS Acute, Teaching, Specialist, Mental Health, and Community Trusts in England. This data is obtained through Define software used by pharmacists for cost saving initiatives, audits, supply issues and service improvements and to compare prescribing practices against other Trusts.

This dataset has been used to investigate drug usage and reports for using this data to investigate drug usage have been provided by the Define software supplier, Rx-Info (which feeds into SCMD).

This dataset was used to evaluate trends in isotretinoin use in secondary care.

Coverage

SCMD includes data from all NHS Acute, Teaching, Specialist, Mental Health, and Community Trusts in England.

Limitations and caveats of SCMD for investigating isotretinoin usage

- The data from April 2022 is provisional and subject to change until the final yearly file has been published for each financial year, the following year.
- Data is from NHS England and secondary care sites only.
- Primary sources are loaded from hospitals daily to the live dataset, but secondary sources appear monthly in arrears of up to 6 weeks.
- NHS trusts may switch to newer pharmacy stock control providers which happened in 2023. Integration of pharmacy stock control systems to capture data is currently being facilitated, potentially causing existing data gaps which will be made available as integration is completed.

- Where specific medicines do not have a dm+d code, they cannot be standardised across all organisations and do not appear in this dataset. This should not impact isotretinoin.
- The dataset does not contain NHS prescriptions supplied by the hospital and then dispensed in community pharmacy.
- Data is at the VMP level which is not as specific as it could be. This should not impact this investigation.
    - VMP in the dm+d model can be defined as "*the first level within dm+d. It describes the abstract or generic medicinal product".* i.e. isotretinoin 20mg capsules.
- Negative values can appear in the data for medicine where supply made in the previous month has been returned in the previous month can be shown of a Trust.
    - There were ~40 negative Virtual Medicinal Product (VMP) quantity values of ~17,000 VMP quantities per month per Trust entries on isotretinoin.
- Some informative fields are excluded from the data; breakages, damages, disposals, expired stock and stock adjustments which would all not be issued to patients, non-NHS general sales, private patients (as non-NHS spend), internal stock transfers which would prevent double counting, GP prescriptions (which could be obtained through other sources).
- During data quality control, internally highlighted outliers of data points are excluded from release.
    - However, a few decimal entries for quantity by VMP per Trust site were included in the raw data, identified manually, which may be explained as data flow or entry errors.
- Where total quantity is zero, data for VMP that month from the concerned Trust are excluded from release as this occurs as an artifact of the backtracking process.
    - This can be seen for some isotretinoin 40mg capsules and gels which have been discontinued yet occasionally reappear after. For this reason 40mg and gels were not included in the stratified by VMP unit quantity graph.
- Outside a single VMP, the quantity values may not be comparative and therefore, may not provide accurate reporting when VMP levels aggregated.
    - Daily defined dose, as defined by WHOCC (30mg), was therefore used to standardise this value for oral isotretinoin and aggregate isotretinoin-containing VMP units, as per a report produced by Rx-info on using their data to investigate usage.

Results

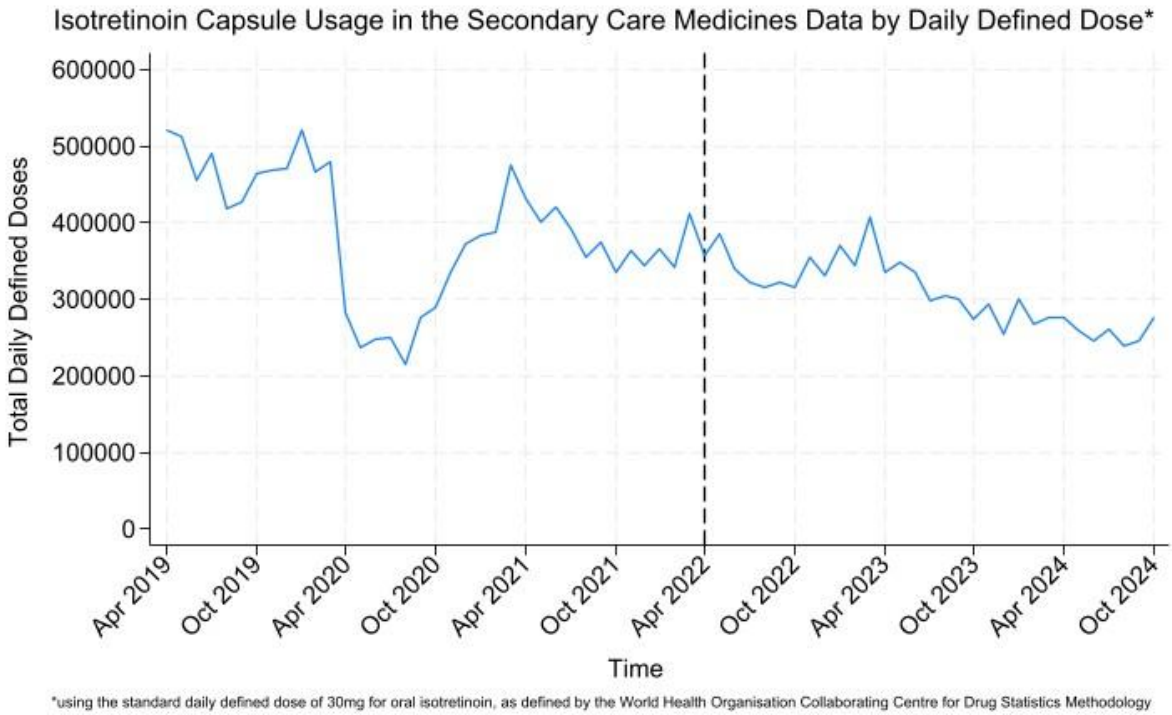


Figure 9. Isotretinoin Capsule usage

Figure 9 illustrates the monthly usage of isotretinoin taken orally in the Secondary Care Medicines Data, expressed in Defined Daily Doses (DDDs). The data includes isotretinoin capsules of various strengths (5 mg, 10 mg, 20 mg and 40mg), converted to DDDs using the standard DDD of 30 mg for oral isotretinoin, as defined by the World Health Organisation Collaborating Centre (WHOCC) for Drug Statistics and Methodology. The Y-axis represents the total DDDs, providing a standardised measure of drug utilisation over time, while the X-axis shows the calendar months. This approach allows aggregation of single isotretinoin-containing VMP levels (where quantity values may not be comparative and therefore may not provide accurate reporting) and for consistent comparison of isotretinoin usage across different periods. The dashed line represents when Secondary Care Medicines Data changes from finalised to provisional data (April 2022). Caveats for this change are presented above.

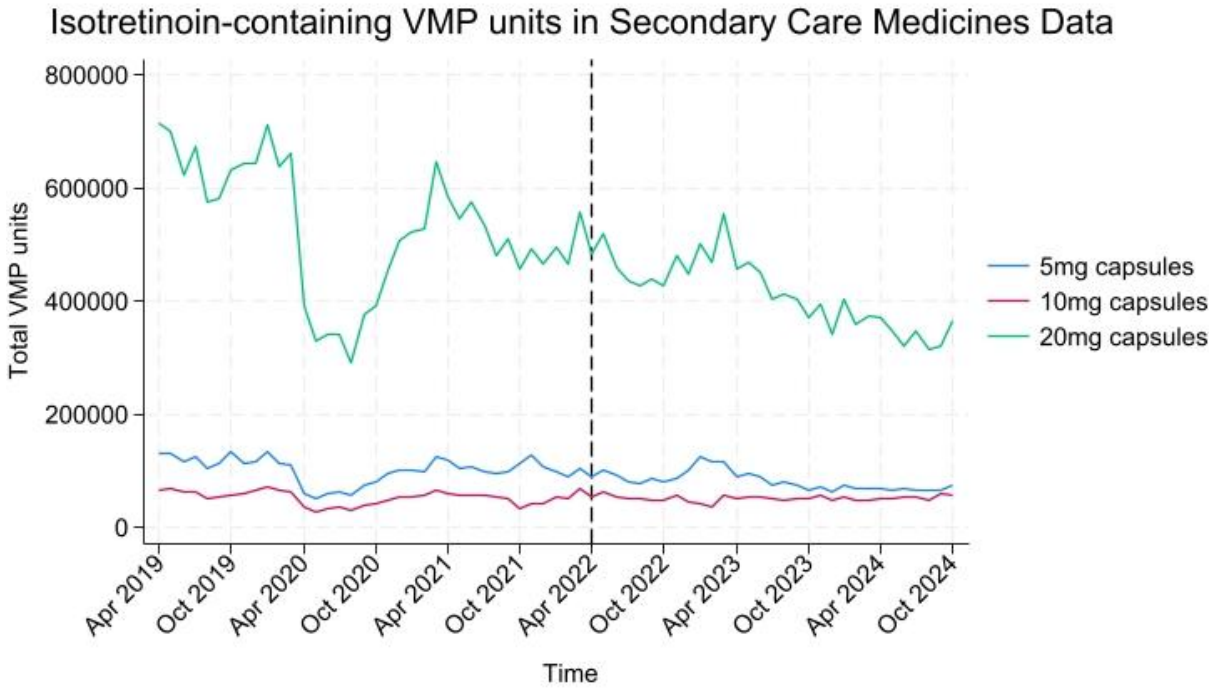
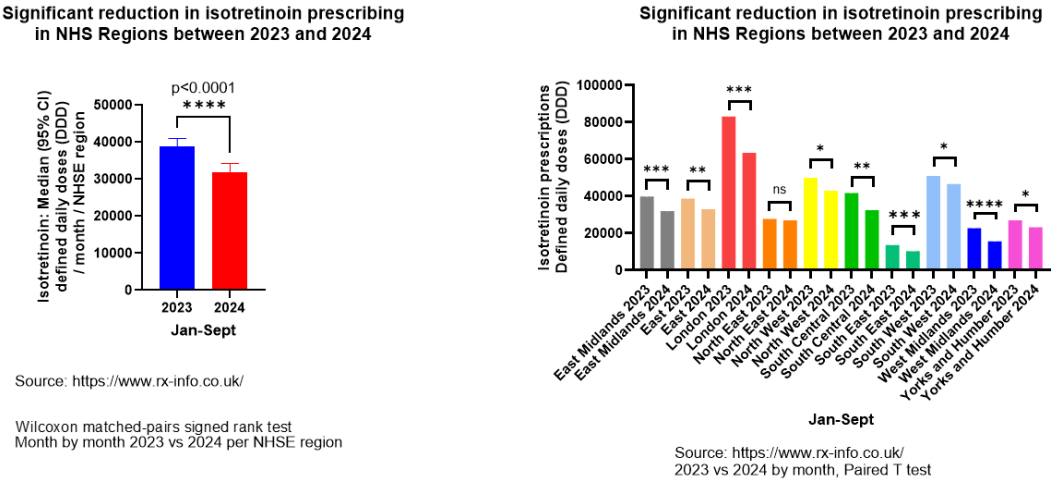


Figure 10. Total quantity of Isotretinoin-containing VMP units for 5mg, 10mg and 20mg only

Figure 10 illustrates the aggregate total quantity in a VMP unit (i.e. 5mg isotretinoin capsules) across Trusts within the Secondary Care Medicines Data for each month. The top line is 20mg, the middle line is 10mg and the bottom line is 5mg. The dashed line represents where the Secondary Care Medicines Data becomes provisional (April 2022).

The pandemic affected medicine usage patterns, supply chains, and stock levels which can be observed in 2020. Overall, there has been a declining trend in isotretinoin usage patterns since 2019 largely driven by the 20mg tablet.

Recent data was received from the BAD providing Define data on hospital prescribing showing a drop in prescribing of isotretinoin from 2023 to 2024 (January to September of those years), see Figure 11. Note Figures 9 and 10 show a significant decline prior to October 2023 which seems to initiate in April 2023. Hence the BAD figures would incorporate a drop in prescribing which began before the implementation of the regulatory measures.



Data from hospital prescribing: DEFINE data set

Figure 11. Data from the BAD based on hospital prescribing DEFINE data set

4.4 Feedback following implementation

The MHRA has been in regular contact with the three devolved nations, partner organisations (for example, the Royal Pharmaceutical Society) and stakeholders following implementation of the new requirements to enable us to better understand how the new requirements affected services. All feedback relevant to implementation is described below.

4.4.1 Qualitative feedback

We received qualitative feedback from the devolved health services nationally and stakeholders, with themes and quotes included below.

The themes identified are:

- Longer appointment times (due to completion of the Acknowledgment of Risk form with associated explanation of risks and benefits)

- Increased waiting lists (for the reasons above, and whilst reconfiguring the services, to accommodate two prescribers and also due to the guidance on suitable prescribers of isotretinoin).

- Increase in patients who have declined treatment (unknown numbers) due to fears about sexual function adverse events (e.g. erectile dysfunction) particularly young male patients. (Patients would generally not have been counselled on sexual dysfunction before.)

- No reports of harm but reports of more severe scarring and low mood due to delays. Two Patient Advice and Liaison Service complaints.

- Move from completely telephone clinics with photographs to face to face clinics.

- Ongoing concerns about private practice (see below).

We do not have any robust quantifiable data to establish the extent of any of these issues.

Feedback suggests that NHS organisations are enforcing the MHRA requirements and NHS dermatologists are adhering to the requirements. The NHS hospitals are finding the requirement to undertake a face-to-face review one month post-initiation challenging (however this is guidance and not a regulatory requirement). This is owing to clinic capacity and the longer appointment times needed to go through all the paperwork and counselling. They have also noted that waiting lists for the acne clinics are long because many had to initially suspend the nurse-led clinics. Allowing Band 7 nurse to prescribe has eased pressures within clinics.

There are also ongoing concerns with private practice with reports and evidence that prescribing in the private sector does not adhering to the MHRA requirements. Owing to the lengthy waiting times for a NHS appointment, patients are being seen in the private sector where prescribers are initiating isotretinoin without completing the Acknowledgement of Risk form. There are reported cases where patients under the age of 18 years were started on isotretinoin by in the private without the agreement of a second prescriber. There is another case of a pharmacist in a private hospital concerned that they were receiving very few prescriptions for dispensing and that patients were being directed to an external community pharmacy. One private hospital has shutdown dermatology completely.

Additionally, positive feedback has been received from pharmacists, in relation to the informed consent obtained during the consultation facilitated by face to face consultations.

Feedback from an ICB in England

'Acne Primary Care Proforma.
In general, primary care have not had any problems in completing these forms. Early on, during the transition to these Acne Primary Care referral forms some of the forms were rejected, this was usually due to the referral being made without the use of the proforma. However, now that this has been embedded into practice, there hasn't been any issues with the proforma.

There was some unease from colleagues in primary care about being a secondary signatory for a specialist drug for which they don't have experience of. There have also been mixed feedback with regards to the patient's past and current mental health. There are some concerns that had been raised with GP practices that there are times when completing this element of the primary care proforma that they don't always have full access to System one or EMIS which would have additional information from secondary care settings they can refer to.

The paediatric dermatology only accept acne referrals when the proforma was used. Whilst compliance has generally improved, the ongoing GP ballot on working to rule may impact the completion of these proformas, as it not specified in the GP contract'

Feedback from an NHS Trust

‘Two prescribers

The counter-signatory requirement has had varying impacts across departments. In paediatric dermatology, where the rule is strictly enforced, finding a second signatory can be time-consuming and may occasionally necessitate asking patients to return for a follow-up visit. This requirement also impacts clinic flow, pulling staff from other responsibilities and potentially delaying subsequent appointments. Although the delay is generally between 5-15 minutes, even this small increase in time can affect the overall clinic schedule.

Despite these challenges, the requirement has not prevented paediatric patients from starting isotretinoin treatment and this was not necessarily the intention of the regulatory requirements rather better information was requested by patients to inform their decision making. The presence of a large team with experienced consultants, trainees, and Band 7 nurses has ensured that delays are manageable. However, the broader impact on clinic efficiency and patient experience should not be underestimated.

Moreover, while about 50% of GPs agree to act as the second signatory, this still leaves a significant number of cases where additional coordination is required within the dermatology department.

Acknowledgement of Risk Forms

Time Impact:

The new Acknowledgement of Risk Forms take an additional 5 – 7 minutes to complete during clinic appointments. This extra time has caused clinic delays, particularly in adult dermatology. However, the information provided in the forms is viewed as beneficial, particularly in enhancing the Pregnancy Prevention Programme, allowing for longer prescriptions and reducing the frequency of required visits for some patients.

Patient Reactions and Discussions:

While the new forms have not drastically changed the way risk-benefit discussions occur, they have standardised the conversation around specific concerns, such as sexual dysfunction. The adult dermatology team uses initiation stickers in clinic to summarise key side effects, reinforcing the information in the Acknowledgement of Risk Form

Difficult discussions around potential side effects re sexual function with young people who are not sexually active. It is essential to discuss this at initiation and follow up but feels inappropriate for those young people who have already identified that they are not sexually active. These discussions may actually be exacerbating / increasing anxiety and causing or contributing to sexual dysfunction. The patient may worry the medication may impact on them rather than it proving to be a true medication side effect.

Sexual dysfunction is now mentioned on the side effects questionnaire, which initially makes this easier to broach the topic of conversation however, a number of nurses are not confident/competent in offering advice if the young person informs they are experiencing this side effect.

There are also concerns that whilst it is important to outline all potential side effects, there is the concern that there are some young vulnerable patients (especially in the paediatric population) where this may deter them from accepting a medication that is excellent with great results.

The multiple forms / need for 2 prescribers and face to face appointments has generated initial anxiety and when seen for follow up patients/ parents have commented about how worried they were initially vs how straight forward taking it has been.

The introduction of the Acknowledgement of Risk Formhas also led to an increase in patients requesting to be seen alone, which is good practice, but further prolongs appointments. While the form has standardised communication, the emphasis on side effects, such as headaches, and hair loss seem to be disproportionate compared to other dermatological drugs like methotrexate.

The document is much more thorough, even though the discussions that previously took place prior to the new updated requirements with isotretinoin were comprehensive, the average acne consultation now takes 30 minutes with 15 minutes to complete the form. Currently appointment times do not reflect this.

If considering isotretinoin, some prescribers may give the patients/families a copy of the ARF to take away and return for another appointment. This has made completing it at the next appointment a lot quicker. However, has generated two appointments rather than one.

Overall, discussions about the risks and benefits are likely to be more consistent between clinicians (within and between departments). The classification about the Pregnancy Prevention Programme status has been helpful. The opt out was not well defined i.e. its purpose, whereas the three categories are much clearer and make a distinction between different forms of contraception.

Pharmacy Perspective:

Initially, the pharmacy team faced challenges during the transition, particularly in clinically screening prescriptions. There were instances of missed or incorrect Pregnancy Prevention Programme endorsements, and the supply request for isotretinoin did not always match the Pregnancy Prevention Programme status. However, the situation has since improved, and now, interventions are rarely needed as prescriptions are generally correctly endorsed and the new process has been fully embraced by both the prescribing clinicians and the pharmacy team.

Face to Face and Telephone Clinics

Adult dermatology teams continue to utilise a mix of face to face and telephone consultations. The challenge faced for the adult dermatology team was the initial meeting to be face to face as this was moved during the COVID-19 pandemic to telephone consultations. Whilst the face to face follow ups at four weeks are challenging due to clinic capacity, telephone appointments remain a valuable tool for ongoing patient management.

Paediatric dermatology has consistently maintained face-to-face appointments, even with the new MHRA guidelines. The additional workload associated with face-to-face follow-ups, particularly for patients in Group C who require pregnancy tests four weeks post-treatment, has been a challenge. Allowing remote follow-ups for appropriate cases, such as stable patients requiring only a urine pregnancy test, could alleviate some of this burden.

Removing the mandated pregnancy testing for Group A, patients has been a positive change, reducing unnecessary clinic visits and easing patient anxiety. The clearer distinction between different Pregnancy Prevention Programme categories has also improved the process.'

Note that there have been no changes to the information GPs should provide at referral. During the healthcare briefing session for the IEWG report in April 2023 it was recommended that the Implementation Advisory Group could consider a referral template so that all the relevant detail can be provided by the referring clinician prior to assessment. This was in response to a comment by clinicians that often there is not enough information in the referral letter, with no details on dose and duration for all acne treatments tried prior to

referral. The BAD then developed an Acne Referral Proforma which can be adapted for local service platforms to help GPs; however they are under no obligation to use this.

4.4.2 NHS England (NHSE) Impact Assessment

The impact assessment was based on modelled data. Although the regulations had been in place for several months. This modelled data was subsequently extrapolated to the whole of England. Further details of the data inputted into the model were requested and are limited:

"The modelling shows the need for about 1000 additional face to face appointments in a county (population 750,000) which is a 5% increase in follow up capacity. For England this represents around an additional 75,000 appointments."

"The modelling numbers included in this document in the columns are from a review of data from my Trust, (serves population of 750 000). I obtained prescribing data about the number of people started on isotretinoin in 12 months (2023), male female ratio and number of under 18s. I have used this to model the impact of the implementation guidance. The number of patients is therefore accurate."

The NHS England modelling assumes that patients must have two appointments with the Lead Prescriber in order to ensure a 'cooling off' period in order to fulfil the requirements of the revised SmPC, so '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'.

However**,** the "Summary of responsibility in isotretinoin care pathway" in section 2.4 of the IIAEWG report states that:

'Ideally, some aspect of information provision should occur at the time of referral (usually from primary care), noting that the final decision on whether to prescribe will be made by the specialist. Information may be given through sharing or signposting to patient educational materials, including the Isotretinoin Patient Guide (developed by the BAD and hosted on their website) or the Oral Isotretinoin Guide for Young People (developed by Medicines for Children, RCPCH). Giving information at the time of referral will create the opportunity for patients and their parents or carers to reflect on the information about isotretinoin and ask questions if isotretinoin is prescribed. Information materials can be used to facilitate discussion and should be available for the patient to take with them or access at home.'

This means, in practice, GPs are not mandated to provide any information, however, they are encouraged to provide or signpost to the patient leaflets listed above, so that the patient has a chance to read these and time to reflect about potential treatments. There have been no other changes to what is being asked of primary care services, except the optional possibility of a primary care Healthcare Professional acting as a second prescriber. It should

also be noted that face to face appointments were recommended by the IIAEWG as best practice but remain guidance, are not a regulatory requirement and are not required within the SmPC. For example the BAD referral proforma covers information provision to the patient by primary care.

There have been no changes to what is being asked of primary care services, except the potential for a primary care healthcare professional to act as a second prescriber if they agree. The 'cooling-off' period between information provision and prescribing the treatment does not require additional appointments (for example, the information can be provided by signposting to acne treatment leaflets at the time of referral, usually in primary care). In addition, not every dermatological service uses the same model of operating, so extrapolating across the country will be challenging. The before-after paradigm may not be accurate as there was significant variation across the UK prior to the recommendations, for example patients were sometimes not seen at all following the first appointment.

With regards to the modelling itself, the strengths are that it takes a detailed approach by breaking down time for specific tasks for each phase of care and the methods include detailed calculations for the additional healthcare professional hours and appointments required, which are clearly derived from patient volume and specific appointment requirements.

However, some limitations of the modelling are that the calculations assume that the numbers of patients and methods of care will be the same across England as for the model county, as noted previously. However, we would expect some areas may have higher or lower referral rates for isotretinoin due to differences in demographics, and that there would be regional differences in specialist dermatology services, which might significantly affect the resource implications.

There are no sensitivity analyses to account for variability in key aspects, such as the proportion of patients initiating isotretinoin under 18 (assumed to be approximately 20%), patients opting out of the Pregnancy Prevention Programme, or additional time required for mental health assessments. This makes the modelling less robust to uncertainty and limits its reliability for decision-making. While additional HCP hours and appointments are quantified, there is no translation into costs (e.g. staffing costs per HCP hour or per appointment). Without this, it is difficult to fully understand the financial burden of the changes.

4.4.3 Private providers

Two major private providers of healthcare were contacted and no specific concerns or changes to volumes of prescribing had been observed. Dispensing patterns do not appear to have materially changed. The Independent Healthcare Providers Network and the Independent Doctors Federation were also contacted to seek data on implementation.

The lack of data sources from private providers limits our understanding in this sector which is being used increasingly by patients to access treatments such as isotretinoin, due to the long-standing waiting times for dermatology appointments.

4.4.4 Royal Pharmaceutical Society

The majority of the concerns raised with the Royal Pharmaceutical Society related to queries about the Pregnancy Prevention Programme, confusion around the duration of treatment, confusion with other oral retinoid Pregnancy Prevention Programmes, who can prescribe retinoids and the validity of prescriptions. As a result, the Royal Pharmaceutical Society published guidance to give more detail on oral retinoid Pregnancy Prevention Programmes.

4.4.5 International regulator positions

Other regulators were contacted to find further information on the work that they were undertaking and assess whether they had similar positions on psychiatric side effects and sexual function. Most regulators have undertaken recent assessments and both side effects are listed in MAH information. Health Canada's safety review[5] concluded that a link between isotretinoin and the risk of sexual dysfunction, including persistent sexual dysfunction after drug discontinuation, could not be ruled out. Health Canada stated that they will work with the manufacturers to update and align the product safety information for all isotretinoin-containing products to include the potential risk of sexual dysfunction, including persistent sexual dysfunction after drug discontinuation. The Therapeutic Goods Administration, Australia, introduced new safety warnings for isotretinoin in April 2025, to include advice to conduct a mental health assessment for all patients before starting isotretinoin, what to do if mood-related changes develop, and new warnings and advice were added regarding sexual health-related side effects.[6] No regulator plans to introduce two prescribers.

[5] Health Canada. Summary Safety Review - Isotretinoin - Assessing the Potential Risk of Sexual Dysfunction, Including Persistent Sexual Dysfunction After Drug Discontinuation - Drug and Health Products Portal (Accessed 12 December 2025)

[6] Therapeutic Goods Administration (TGA). New safety warnings for isotretinoin (Roaccutane). Medicines Safety Update. Published 7 April 2025. https://www.tga.gov.au/news/safety-updates/new-safety-warnings-isotretinoin-roaccutane (Accessed 30 September 2025).

4.5 The British Association of Dermatologists (BAD) concerns

4.5.1 Overview

The BAD is the professional membership body for dermatologists in the UK. The BAD have submitted a dossier to this review including surveys of dermatologists and patients and a literature review.

The BAD main concerns are that:

- the new recommendations and regulatory requirements are disproportionate to the scientific weight of evidence and that the reduced access to isotretinoin and increased emphasis on unproven risks causes anxiety and is harmful.
- the evidence base underpinning these new restrictions is not robust.
- the new recommendations are having negative consequences for non-acne dermatology patients.
- the additional burden on the NHS caused by the new recommendations is not justifiable at a time when the government's priority is to reduce waiting lists.

They have requested several changes to both the new regulatory requirements and associated IIAEWG guidance, including:

1) removal of the requirement for a second healthcare professional's approval for isotretinoin prescribing in patients under 18 years **(regulatory)**
2) removal of the requirement to discuss sexual function at baseline and every follow-up appointment **(regulatory)**
3) removal of the requirement for face-to-face follow-up appointments (guidance in implementation report)

In addition, the BAD requested:

4) modification of the Acknowledgment of Risk form **(regulatory)** to make it shorter and more flexible to use.
5) reinstatement of MHRA guidance for remote pregnancy testing.

Each request and associated submission will be outlined below.

New data submitted to the MHRA on 31 January 2025 from the BAD:

- Getting It Right First Time (GIRFT) programme data suggests an increase in 40-52 week waits from October 2023 to October 2024 in 0-18 years olds for all dermatology services. [Note this does not isolate acne referrals, although this is likely to be a significant proportion of referrals. In addition, the starting point for comparison should

be approximately six months later, which was the guidance timeframe given by the BAD for implementation to be embedded in dermatology services].

- DEFINE data set and FP10 prescription forms data appear to show a reduction in isotretinoin prescribing between 2023 and 2024 (graphs from the Bennett Institute for Applied Data Science). [Note that this does not show any data prior to 2023, which would have provided context. There are concerns with the DEFINE data because it includes the whole of 2023 and yet a significant drop was seen in the data in the period between April and October 2023].
- Further qualitative (dermatologist survey) data outlining logistical difficulties with the second prescriber particularly in rural or district general hospital or private/independent provider settings or due to staffing shortages. Some dermatologists have reported a reduction or cessation of prescribing isotretinoin in the under 18 age group. Also, that the average extra time for a consultation in this age group, following the regulatory changes is reported to be 20 minutes.

4.5.2 Request for removal of the requirement of the second health care professional (regulatory)

4.5.2.1 The BAD concerns and proposal

The BAD request for removal of two prescribers in under 18s is as follows:

Two-HCP approval for under-18s

This is a highly contentious aspect of the new recommendations. The BAD pilot survey in January 2024 identified that 87% of members were opposed to this change. The IEWG April 2023 report acknowledges there is a lack of evidence for an increased risk of serious side effects in this age group.

Evidence

Historically, the incidence of suicide reported on the yellow card system is higher in those over 18. A recent meta-analysis suggests at a population level, there is no increased risk of suicide or psychiatric conditions in those using isotretinoin, for all age groups. In fact, treatment of acne with isotretinoin both in mixed and under-18 age groups has superior neuropsychiatric benefits, associated with improved overall mental health, and reduced depression and insomnia, at the population level compared to oral antibiotics.

New population data also suggests there is no link between isotretinoin and sexual dysfunction. A systematic review investigating the potential association identified that existing data was of very poor quality, with many studies demonstrating low methodological rigour.

The purpose of the two-HCP approval was not explicitly stated in the IEWG report and could not be clarified in subsequent discussions with the MHRA. The report states “that until further data on the level of risk could be established in this age group, there should be greater oversight of these patients” due to inconsistencies in monitoring of patients of all ages. New, reassuring data has been published since the ratification of the IEWG report, and the modified changes proposed by the BAD in collaboration with the MHRA will improve the monitoring of all patients, obviating the need to discriminate against under-18s.

Implementation impact

The two-HCP approval has not improved safety or changed outcomes for under-18s. The BAD member survey in July 2024 identified that of 486 respondents, 343 had initiated isotretinoin on a median number of eight under-18 patients since implementation. Of the >4000 patients initiated, there were only two cases of initial disagreement (one for an irrelevant soya allergy and one for a nuance regarding mental health). Both of these patients went on to successful isotretinoin initiation. The 100% agreement rate (initial disagreement <0.05%) demonstrates the process does not influence clinical decision-making or change practice.

The burden of the two-HCP approval requirement for under-18s has been significant, with a negative impact on patients and services. Dermatology departments are over-stretched with the waiting time for a new appointment in the UK averaging from 60 weeks to 6 years. Paediatric dermatology services are under even greater strain.

The two-HCP approval process requires a further opinion from a consultant or specialist colleague which takes time out of busy clinics in those working within a team, or a second new patient appointment in those who do not, for example in the smaller District General Hospitals. Other means include the multidisciplinary team meeting (MDT) requiring regular time commitments from multiple clinicians and administrative resources to collate case histories and photographs. Together this has a negative impact on dermatology services in general, affecting all patients, including those with skin cancer.

The two-HCP approval requirement creates barriers to access to care for young people with severe acne. According to the BAD impact survey, 71% of respondents report delays in initiation of treatment for this vulnerable age group and the pilot survey identifies 12% of respondents have ceased prescribing to under-18s altogether.

There is consistent feedback from dermatologists that the requirement induces disproportionate anxiety and fear in young people and parents, who may decline treatment where there are no suitable alternatives. This is concerning, given the mental health implications of inadequately treated severe acne and its sequalae, such as permanent scarring and pigmentation, often on the face. These disproportionately impact young people and patients with darker skin tones.

Additional arguments for change

The two-HCP approval requirement is inconsistent with other systemic medications, including cytotoxic drugs, (which are used to manage paediatric dermatology patients with severe skin disease) that do not require a second HCP. It undermines the doctor-patient relationship, clinical decision-making, and professional autonomy.

Proposal for change

The BAD propose that the requirement for two-HCP approval for under-18s is removed. Inconsistencies in monitoring can be addressed by implementing a strong regulatory framework and other support mechanisms tailored to the patient, parents and clinicians. The BAD is committed to developing webinars and information videos in full collaboration with the MHRA to achieve this.

4.5.2.2 Purpose of two prescribers

Isotretinoin is authorised for treatment of severe acne that has failed to respond to antibiotics and topical treatments, and it should not be prescribed as first line or in moderate or mild disease. However, there have been cases where isotretinoin has been prescribed

inappropriately to those who did not have severe acne, and without adequate courses of standard therapy.

The IEWG heard from stakeholders that there was particular concern about the lack of awareness of sexual side effects and of the potential long-term nature of some side effects. and that the side effects are unpredictable and can occur suddenly leaving patients vulnerable and the families lost, not knowing what to do.

Concerns were raised that adolescents may be more susceptible to side effects due to their developmental stage. There were also concerns that adolescents may not fully comprehend the risks prior to treatment, and that isotretinoin was prescribed inappropriately. Equally it was highlighted that delaying treatment for severe acne, which may particularly affect adolescents, could be associated with long term scarring which may be associated with significant psychological harm.

Though 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. In balancing these views, 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.

4.5.2.3 Discussion

As referred to earlier there is no high-quality quantitative data to establish the impact of the regulatory requirements. The NHS England impact assessment is based on projected figures despite the regulatory requirements being in place for several months and it also makes a number of inaccurate assumptions of the regulatory requirements. Consequently, we have to rely on other sources such as stakeholder feedback. The BAD is a key stakeholder and crucial to the successful implementation of the regulatory requirements.

There are longstanding delays to dermatology services, and it is challenging to isolate and quantify the impact caused by the requirement for two prescribers in under 18’s, coupled to the extension of appointment times by a more comprehensive counselling of risks and new risk management materials. Trusts have implemented the two prescribers for under 18’s in various ways including through the approaches suggested by the IEAWG such as a multi-disciplinary approach, or by seeking sign off during the clinic session.

The original driver for the additional oversight in the under 18’s was the concern that this age group may be more susceptible to the psychiatric and sexual side effects of isotretinoin and that adolescents may not fully comprehend the risks prior to treatment. Given the uncertainty, the CHM recommended that until further data on the level of risk could be established in this age group, additional oversight was required. The review of recent scientific literature in section 3 of this paper does not provide robust new evidence though the studies are large, and it is unlikely that better studies will be published in the near future.

The Acne-ID trial has just started recruiting patients, but results are unlikely to be available soon. The protocol for the MAHs' PASS is still being developed and on its own is unlikely to provide sufficiently robust data to further characterise the risks, nor provide sufficient reassurance on safety, to lift restrictions.

The BAD believe that the additional safety net provided by the second prescriber is negligible due to the parallel strengthening of other safety measures. A survey sent to 2380 the BAD and the British Society for Paediatric and Adolescent Dermatology (BSPAD) members in July 2024 showed that of 486 respondents, 343 had initiated treatment in patients under 18 since the new recommendations were introduced. (This was estimated to amount to more than 4000 patients who were initiated on isotretinoin by the respondents.) There were two reported cases of second prescriber disagreement (one disagreement was due to a soya allergy and the second was due to an aspect of mental health). Whilst this shows that there is very limited disagreement between the lead and second prescriber, it is not possible to determine if the additional oversight has improved the consistency of initial prescribing. It remains a concern however that adherence to the second prescriber requirements may be limited in private practice and that delays in treatment may be driving more patients to access isotretinoin through this route or possibly further delaying access through the NHS.

The measure was introduced approximately one year ago and many services in the NHS have now reconfigured their services to accommodate the changes, and it will likely cause more disruption and confusion to reverse. We have not heard concerns from directly from patients on the Acknowledgement of Risk form. There are no concerning yellow card reports. However both the BAD and skin doc have conducted patient surveys, which particularly highlight patient satisfaction as a result of accessing isotretinoin treatment remotely. However, it is unknown if this is representative of wider patient views.

The BAD have proposed including a statement on the Acknowledgement of Risk form that patients are entitled to a second clinical opinion regarding their treatment instead of the requirement for a second prescriber. Such a proposal is unlikely to stop inappropriate prescribing as patients are unlikely to seek this option. For example, the onus is on the patient to request a second opinion, and the patient would have to be confident to do so. In addition, many patients want to access this medication and may have waited many months and would not want further delay. Patients who have been inappropriately prescribed this medication would not be aware of this second prescriber option, and in the private sector a second opinion would represent additional cost which few patients would voluntarily seek.

It is important to also highlight that the right to ask for a second opinion is available to all patients and that the GMC states that doctors must 'respect the patient's right to seek a second opinion'. This was an option to patients prior to the new measures introduced in October 2023 albeit one that patients are unlikely to seek as noted above. Therefore, it is unclear whether this will provide the additional oversight considered necessary by the CHM.

It is challenging to establish whether the introduction of a second prescriber has improved the safety of isotretinoin prescribing primarily as there is no evidence or distinct data source

to evaluate the impact of this measure. We have no access to patient responses on the Acknowledgement of Risk form or on follow up consultations. Undoubtedly completion of the Acknowledgement of Risk form will raise awareness as to the potential side effects with patients taking isotretinoin and follow up visits will better monitor side effects. Nevertheless, independent NHS stakeholders have been uncertain about any improvements in safety as a result of the introduction of the second prescriber when asked.

The MHRA will continue to monitor the scientific literature for further evidence of the level of risk on sexual function and psychiatric side effects as part of routine pharmacovigilance. The results of the imposed PASS, a self-selection study asking young people to report side effects directly through a web platform, is designed to provide some additional evidence. To provide reassurance to lift the restrictions we would ideally need further well-designed prospective studies which complement the PASS and also address the limitations of the studies assessed in the updated MHRA literature review. However, it is uncertain whether such studies will become available and are unlikely to deliver information in the short-term. In the longer term, the ACNE-ID trial may provide some useful information on use of a lower dosage of isotretinoin. The trial will also look at side effects and other measures, such as patient reported acne severity, satisfaction with treatment, and mood monitoring, during the trial, related to the different dosages. This may provide good evidence on whether a lower dose can be used for similar efficacy but with an enhanced safety profile.

4.5.3 Removal of the requirement to discuss sexual function at baseline and every follow-up appointment (regulatory)

4.5.3.1 The BAD concerns and proposal

The BAD request is as follows:

Monitoring of sexual dysfunction

The association between isotretinoin and sexual dysfunction is tenuous and reports are very rare. The IEWG maintains that a causal link cannot be established. However, personal anecdotal accounts of sexual dysfunction felt to be associated with isotretinoin were voiced directly to the IEWG by some patients. It is recognised the absence of evidence does not completely eliminate a potential association, but responsible guidance must reflect the available data and provide context to enhance patient understanding and inform consent.

Evidence

New evidence has emerged since the publication of the IEWG report, corroborating that any association between isotretinoin and sexual dysfunction remains very weak. [7] Further recently published population-based and other studies support the absence of a causal link between isotretinoin and sexual dysfunction. [6] Together, this suggests that if a direct or indirect link does exist, then the clinical risk of sexual dysfunction is very rare.

Of significant concern is the 'nocebo' effect, a real phenomenon where negative expectation causes a detrimental effect. This concept has been validated in patients taking finasteride[8] and beta-blockers. [9] Those informed about the risk of sexual dysfunction were more likely to experience these

side effects compared to those who were not given the information. In the case of isotretinoin, placing undue emphasis on the unproven, very rare risk of sexual dysfunction may actually induce it, causing unnecessary harm. This unintended consequence was not considered in the development of the guidance.

Implementation Impact

Only 20% of the BAD members surveyed in our Pilot Survey were in favour of the requirement for discussion about sexual function concerns at baseline and at every follow-up. Discussions around sexual function and monitoring at every follow-up appointment take a disproportionate amount of time given the insubstantial scientific evidence, doubling new patient appointment slots from 15 to 30 minutes and significantly reducing capacity. The questions about difficulty getting or keeping an erection, breast tissue development (males), vaginal dryness, change in periods (females), reduced sex drive or other changes in sexual function (males/females), create confusion and unnecessary anxiety. Some patients are refusing treatment despite clear clinical need due to over-emphasis of the risks, and the laborious consent process which does not contextualise the risk.

Additional arguments for change

Medications such as beta-blockers, finasteride and anti-depressants, which have a much stronger association with recognised and known risks of sexual function side effects, have no requirement for an Acknowledgement of Risk (AoR) form or required monitoring at baseline and every follow-up appointment. Nor do other international guidelines specify the need to do so. [10-15]

The USA guidelines do not mention sexual dysfunction at all. The Australian College of Dermatologists states there is currently insufficient evidence to suggest an association exists between isotretinoin and sexual dysfunction, and they will continue to monitor the situation. [12]

The Singapore Health Services Authority states that ‘safety information in the local PIs [package inserts] of isotretinoin products is sufficient to manage the risks of psychiatric disorders and sexual dysfunction. Nevertheless, it would be relevant to remind healthcare professionals who are prescribing isotretinoin of these potential risks and the relevant measures taken.’

Health Canada[15] has specifically reviewed the evidence for sexual dysfunction following the publication of the MHRA regulatory requirements. They recommend that the product safety information for all isotretinoin products in Canada be updated to include information on sexual dysfunction and have informed healthcare professionals about this change. However, no recommendations for further action regarding counselling or monitoring were indicated.

Proposal for change

The BAD believes there is justification to remove the requirement for sexual dysfunction monitoring altogether. However, we recognise this would require a revision to the SmPC. To avoid this, we suggest improved contextualisation of the weak evidence and rare risk which may link isotretinoin and sexual dysfunction.

We suggest patients and parents (if appropriate) be given information on the rare risk of sexual dysfunction at baseline and that they are monitored at the first follow-up appointment. If no issues are reported, patients should be asked to raise new issues with sexual function at future dermatology appointments. If issues are reported, appropriate pathways should be followed with continued monitoring at future appointments.

Clinicians will be able to tailor the process to the individual patients through the following actions:

• Changes to the language and structure of the AoR form (see section 3.3).

• Increased flexibility on how questions are asked at baseline and follow-up.

• Changes to the frequency of monitoring.

• An addendum to the April 2023 IEWG report to highlight these changes; the BAD has agreed to disseminate guidance to its members on any such addendum. The BAD would also produce supportive information videos for patients, parents and clinicians.

4.5.3.2 Discussion

The counselling and monitoring of sexual function is a requirement of the SmPC:

'Sexual disorders

Isotretinoin use may be associated with sexual dysfunction (see section 4.8). There have been reports of long-lasting sexual dysfunction where the symptoms have continued despite discontinuation of isotretinoin.

Patients, and where appropriate, parents or carers, must be counselled about the 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 choosing the most appropriate counselling approach, including giving the option to discuss without parents or carers present where appropriate.

All patients should be asked about the presence of symptoms or signs of sexual dysfunction prior to starting treatment with isotretinoin and monitored for the development of new sexual disorders during treatment.'

In the CHM IEWG report, 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, which can continue long term in some patients, and can have a devastating impact on patients and their families. The literature surrounding isotretinoin and sexual side effects is limited.

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 CHM IEWG report suggested monitoring for sexual side effects with isotretinoin could take place via a self-administered questionnaire.

The CHM discussed the complexity of the relationship between acne and possible psychiatric and sexual side effects and the importance of adequate awareness to ensure patients seek and receive appropriate support. Limitations in the available data meant that it was difficult to definitively establish causal associations with either the psychiatric or sexual side effects suspected to be associated with the use of isotretinoin. However, importantly an association could also not be ruled out and the individual experiences of patients and families continued to raise concern.

It was clear that clinical practice varies between services and that there was a need for a more consistent approach so that patients and their families know what to expect and can make informed decisions. Some patients 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. As referred to before, the CHM concluded that the overall balance of risks and benefits remained favourable for patients with severe acne resistant to antibiotics and topical treatments if further action was taken to ensure patients are fully informed about isotretinoin and they are effectively monitored during treatment.

Patients need to be given accurate information regarding the benefits and risks of possible treatments to enable them to make an informed decision together with their healthcare professional. This is also the case when there are limitations in the data preventing the establishment of causal association which is often the case for side effects. Furthermore, patients need to be appropriately monitored during and after treatment.

All patients should be asked about the presence of symptoms or signs of sexual dysfunction prior to starting treatment with isotretinoin and monitored for the development of new sexual disorders during treatment. This is a condition of use of the medicine and is outlined in section 4.4 of the SmPC (special warnings and precautions for use). The CHM IIAEWG report advised:

'Patients should be given the opportunity to discuss sexual function concerns at every follow-up appointment. This should be age appropriate and follow the same guidance regarding confidentiality and safeguarding as for the initial assessment. Patients should be asked if they have experienced any problems with their sexual function since their last appointment. If the patient expresses concerns, follow up questions should explore problems further and ask about other areas as appropriate including erectile function, vaginal dryness, change in periods, breast tissue development/gynaecomastia, decreased libido, other change in sexual function including genital hypoaesthesia.

A side effects patient questionnaire for patients to complete before clinic appointments, either online or in the waiting room, may be helpful (an example is the Isotretinoin Side-effects Patient Questionnaire which can be adapted locally). This may not be appropriate for young people attending with parents or where online form links may be sent to a parental phone number.

If sexual problems are identified during isotretinoin treatment the HCP should have a discussion with the patient regarding how to manage this, for instance watch and wait approach, dose reduction, stopping isotretinoin, and/or referral.'

The key difference of the revised approach proposed by the BAD is that patients will not be asked about sexual function after the initial follow-up if there have been no issues or concerns. However, prescribers should advise patients to raise any new issues regarding sexual function at a future appointment.

Section *4.1 New research published after CHMIEWG report* of this Public Assessment Report, contains the assessment of new scientific publications on this topic. Thang et al.'s letter to the editor (International Journal of Dermatology, February 2024) regarding male sexual function and isotretinoin exposure, concerns only on those events presenting to healthcare services within a year of starting treatment, meaning there was a high risk of under-ascertainment of outcomes. The authors acknowledge other limitations of their study, including only looking at data from male patients and that future studies are needed to replicate these findings and evaluate whether they generalise to other populations. The MHRA assessment is that these remain preliminary findings and do not warrant a change in clinical practice.

Another key paper published in December 2023, is the meta-analysis by Tan et al. in JAMA Dermatology regarding the 'Risk of Suicide and Psychiatric Disorders Among Isotretinoin Users - A Meta-Analysis'. This meta-analysis was limited by substantial heterogeneity and all studies were highly likely to be subject to confounding by indication and detection bias. As the authors note, whilst the findings are reassuring at a population level, dechallenge-rechallenge studies have provided evidence between isotretinoin and mood changes in some individuals. The relationship here is complex and a risk associated with isotretinoin in some individuals may be masked by the benefits of effective treatment in the broader population in epidemiological studies. The authors conclude that clinicians should continue to practice holistic psychodermatological care and monitor patients for signs of mental distress during isotretinoin treatment.

We note too that Health Canada have recently published a Summary Safety Review[7] assessing the potential risk of sexual dysfunction, which concluded that a link between isotretinoin and the risk of sexual dysfunction, including persistent sexual dysfunction after drug discontinuation, could not be ruled out.

The Therapeutic Goods Administration (TGA) has updated the Patient Information in section 4.4, for health professionals to screen for sexual dysfunction prior to treatment, monitor for symptoms and cease therapy promptly if symptoms develop or worsen, and refer as appropriate.[8] Note that in Australia prescribing of isotretinoin is restricted to specialist physicians and dermatologists only

A key issue reported by the BAD has been use of the term 'not known' with regards to sexual and psychiatric side effects, and that this was very difficult to explain to patients in a clinical context. The BAD are concerned that the risks being presented as 'unknown' are actually 'rare' or 'very rare', and the change of frequency to 'not known' has unduly worried patients. However, there is no robust evidence regarding the incidence of sexual side effects associated with isotretinoin.

[7] Health Canada. Summary Safety Review - Isotretinoin - Assessing the Potential Risk of Sexual Dysfunction, Including Persistent Sexual Dysfunction After Drug Discontinuation. Published 7 June 2024. https://dhpp.hpfb-dgpsa.ca/review-documents/resource/SSR1717527382406 (Accessed 8 June 2025).
[8] The Therapeutic Goods Administration introduced these warnings for isotretinoin in April 2025.

The rationale for the CHM IIEWG report recommendations to revise psychiatric side effects frequencies to 'not known' was that Yellow Card data underestimated the frequency of side effects due to underreporting. The CHM 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. The CHM also 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. The CHM advised that it is important to ensure the message that the level of risk could be greater than previously suggested and could be higher in younger age groups (pp.98-99 IIEWG report).

The MHRA offered to signpost via an addendum on the IIAEWG report webpage to the BAD clinical guidance to make this requirement as pragmatic as possible for clinicians, if the key function of checking for and monitoring of this adverse event is retained. This is deemed to be reasonable as ultimately interpretation of the SmPC is clinical decision, and the BAD is the key professional body setting guidance for dermatology clinical practice in the UK. As noted above, within the BAD suggested framework patients will be asked about sexual function at baseline and at the first follow-up. If there have been no issues or concerns patients will be asked to highlight any concerns to their healthcare professional. However is this sufficient risk mitigation or is there is a need for patients to be proactively asked about sexual function at every appointment (either verbally or through a supplementary side effects questionnaire filled in prior to the consultation)? CHM advice was sought on this matter.

4.5.4 Removal of requirement for face-to-face follow-up appointments (guidance)

4.5.4.1 The BAD concerns and proposal

The BAD request is as follows:

Virtual follow-up appointments

Removal of the face-to-face requirement for follow-up appointments was identified as another priority in the BAD pilot and impact surveys, as well as a change to the prescriptive interval after the commencement of treatment. We suggest alteration from 'approximately 1 month' after initiation to 'within 8 weeks.'

Evidence

Data from the published literature do not support the requirement for face-to-face follow-up appointments with isotretinoin monitoring. Virtual follow-ups have been widely implemented safely and effectively across specialties including dermatology and rheumatology, as well as psychology and psychiatry where they are now included in best practice recommendations. [16-19] Dermatology and rheumatology services regularly use virtual appointments for the monitoring of a variety of systemic treatments.

The first study on ‘mobile teledermatology’ for the management of acne with isotretinoin was published in 2015 demonstrating similar excellent outcomes and near similar efficacy, compared with face-to-face management. [20] During the Covid-19 pandemic, services switched to remote prescribing of isotretinoin, and several publications favourably outline these experiences. [21-23] All describe high patient satisfaction, good outcomes and excellent safety standards based on adverse event monitoring.

There is no evidence for improved outcomes by mandating all follow-up appointments as face-to-face in the management of isotretinoin. This is also true for the requirement for the first follow-up after isotretinoin initiation to be within ‘approximately 1 month’. Clinical judgement is required to determine optimal follow-up care, tailored to the individual patient's needs, and must align with service capacity.

Implementation impact

There is insufficient capacity to see all isotretinoin follow-up patients in person and within the required time frame This has a negative knock-on impact across dermatology services affecting all patients including those with skin cancer. There are also reports that the guidelines have derailed some previously successful digital services, particularly in rural and remote areas which involve long travelling distances, adding to health inequalities and impairing access to care.

The requirement for face-to-face follow-up appointments reduces patient choice and impacts productivity, particularly for patients in school or university, or for patients and parents in work. It also contravenes the NHS green agenda[24] and sustainable travel plan, 25 as well as aims for digital transformation identified in the NHS Long Term Plan, which recommends using remote consultation and monitoring if possible. [26]

Additional arguments for change

No other (recently published) international guidelines specify that follow-up appointments must be face-to-face or that such restrictive timescales must be imposed for the initial follow-up appointment. [10-15]

Proposal for change

Change in the guidance is recommended to allow for virtual follow-up consultations in appropriate clinical circumstances. Flexibility for the first follow-up appointment following initiation is required and guidance should be ‘within 8 weeks’ rather than ‘approximately 1 month.’ An addendum to the October 2023 IIEWG report will be required to implement these changes.

4.5.4.2 Discussion

The IEWG report did not consider the mode of consultation. This topic was introduced at the request of the IIAEWG due to concerns regarding remote providers (e.g. where the patient is never seen in person). The IIAEWG advice regarding face-to-face consultations remains guidance. This guidance is outlined in the report of the Commission on Human Medicines Isotretinoin Implementation Advisory Expert Working Group. It is based upon good clinical practice, safeguarding and GMC principles.

For example, a course of isotretinoin treatment may take on average between 16 to 24 weeks (around 4 to 6 months). Following the guidance, a patient would be seen at the initial appointment, again at approximately 1 month and thereafter approximately every three months. Practically this would mean, during a 6-month course of treatment, a patient would be seen three times (at the initial assessment, at the one-month follow-up, then at approximately 4 months). If patients require a longer course of treatment, then under this guidance they would need to continue to be seen in person every 3 months.

The frequency and mode (face-to-face or remote) of additional follow-up appointments will depend on other factors (including Pregnancy Prevention Programme, mental health concerns, other side effects, dosing, patient preference, and hospital systems).

Face-to-face consultations were specified in the IIAEWG guidance because of concerns raised by the group that patients would be accessing isotretinoin online without ever being seen in person by a doctor or healthcare professional. Indeed, online prescribers often do not have any facility to see patients in person and only conduct assessments remotely. However, it is not a regulatory requirement that is specified in the SmPC.

This issue was highlighted at the CHM meeting in January 2024 as a ‘for information’ item, following communications from a private remote dermatology service provider. Further expert view was sought from dermatology, psychiatry and sexual health professionals including representatives from the BAD teledermatology and British Association of Sexual Health and HIV (BASHH). There was no clear consensus on what best practice is, with significant variation within the specialities and clinical services as to what is appropriate.

The BAD teledermatology representative was a consultant dermatologist who assesses patients initially face to face, but thereafter follows up on the telephone without looking at the patient’s skin again. (When they do review the skin remotely for other conditions, photographs are used because the quality of image on video calling is extremely poor.) BASHH representatives including a consultant sexual health physician were clear that for adolescent patients, reviewing patients face to face would be preferable, to provide optimal safeguarding opportunities. The consultant child and adolescent psychiatrist felt it was not possible to undertake an accurate initial assessment of a young person’s mental health by telephone but it may be possible by video consultation and would encourage initial appointments to be face to face as this allows a more thorough understanding of the patient’s difficulties and challenges. It is also easier to undertake a psychiatric risk assessment face to face than through telemedicine. The psychiatrist did not believe that there needed to be a blanket ban on no video conferencing for initiation of isotretinoin, however, he felt that it should not be the norm for children and young people and that there needed to be clear guidance on what circumstances would make it inappropriate.

The MHRA proposed an explanatory comment as an addendum to the CHM IIEAWG report clarifying that face to face is not a regulatory requirement, but that it was advice from the

CHM IIAEWG and that professional standards and best practice should be followed. Healthcare professionals should consult GMC guidance, and other relevant guidelines and local polices. The BAD has also developed best practice guidance covering the use of remote consultations noting concerns around safeguarding in adolescent patients (particularly around sexual function and mental health).

4.5.5 Modification of the Acknowledgment of Risk form to make it shorter and more flexible to use

4.5.5.1 The BAD concerns and proposal

The BAD request is as follows:

The Initiation/Acknowledgement of Risk Form (AoR)

The five-page AoR form is onerous, impractical and intimidating for patients and parents. Its disproportionate focus on potential and rare mental health and sexual dysfunction risks without the context of common side effects or intended benefits impairs the informed consent process, appears defensive and undermines trust.

Evidence

The published literature does not support the emphasis on rare side effects such as mental health issues or sexual dysfunction. A recent meta-analysis suggests at the population level, there is no increased risk of suicide or psychiatric conditions in those using isotretinoin.

Therefore, listing an exhaustive number of potential mental health consequences in detail, including low mood, depression, anxiety, agitation, aggression, self-harm, suicidal thoughts/attempts, psychosis (loss of touch with reality), is unwarranted, causes undue alarm and risks a ‘nocebo’ phenomenon with subsequent harmful effect. New population data also suggests there is no link between isotretinoin and sexual dysfunction. A systematic review investigating the potential association identified existing data as very poor, with many studies demonstrating low methodological rigour. The emphasis on sexual dysfunction in the AoR form is unjustified and disproportionate and acts as an unnecessary deterrent to appropriate treatment. It also risks potential harm due to the ‘nocebo’ effect.

Implementation impact

The BAD pilot survey indicated changes to the AoR form are a priority for practising dermatologists. It is time-consuming, confusing to use and ineffective. Clinic appointment times have doubled from 15 to 30 minutes in part due to the unnecessary complexity of the forms, with a negative impact on capacity for all dermatology patients, including those with skin cancer.

Feedback from multidisciplinary Lead Prescriber groups describes the AoR form as a 'distracting tick-box exercise' that hinders clinicians from conducting a holistic assessment and consultation with patients, ultimately detracting from the quality of care. Furthermore, unwarranted anxiety and fear are causing some patients and/or parents to refuse treatment with isotretinoin, with unforeseen consequences, as discussed above (section 3.1.2).

The title of the AoR form itself causes unnecessary alarm, as does the double-tick box method, more commonly utilised in a research setting. This adds to the appearance of prioritisation of defensive medical practice over holistic care and undermines trust.

Integration of the Pregnancy Prevention Programme into the AoR form has caused confusion and wastes consultation time in patients for whom the Pregnancy Prevention Programme is not applicable. In practice, a patient may need to arrange for suitable contraception before the commencement of isotretinoin, but after the decision to treat and completion of the AoR form. It is appropriate in this instance for the patient to see a Clinical Nurse Specialist rather than a Lead Prescriber for follow-up, to complete the Pregnancy Prevention Programme section, which is not possible with the form in its current format.

A crucial consideration overlooked in the original development of the AoR form is the space for the patient identification sticker on each page of the document. This creates unnecessary clinical risk for reasons of accurate patient identification.

It is important in clinical practice for the risk form and Pregnancy Prevention Programme aspect to be featured on a single page each and available to fill in electronically, for ease of use and to minimise paper wastage.

Additional arguments for change

A complex AoR form is not required for other systemic medications in UK dermatology or for isotretinoin in other countries.

4.5.5.2 Discussion

The CHM IEWG report recommended that the previous Acknowledgement of Risk form (discontinued in 2023) for female patients should be expanded to cover all potential risks and used for all patients in order that they and/or their parents/carers 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. A revised form was developed by the IIAEWG with emphasis on mental health and sexual function due to the severity of these side effects and the need to mitigate the risk. This form was introduced in October 2023.This form was introduced in October 2023.

The feedback from the BAD is that the current form is long and increases appointment time. In addition, they are concerned that talking about sexual function side effects may lead to some patients declining treatment or it creates a “nocebo” effect, particularly as the frequency is unknown. In a similar way, the BAD feel that providing detail about some of the mental health side effects leads to undue alarm.

Therefore, the BAD proposed a streamlined form. The MHRA and the BAD have worked closely to review the form and taken on board much of the feedback such as:

- moving explanatory information for the patient to the end,
- proposing a separate sheet for healthcare professionals (either at the end of the electronic form or at the top of the paper pack of forms)
- removing some repetition in the pregnancy section.

The original recommendations included better information on side effects to support informed decision making and further information on frequency of psychiatric side effects for patients to understand the uncertainty in this risk and its likely order of magnitude. It is therefore important that any amendments continue to fulfil this original objective and a streamlined form which adopts many of the suggestions of the BAD is proposed. The BAD suggested amendments which retained the message of the original form but in a simplified manner were incorporated into the proposed form and key points are set out below:

- The reminder box on mental health support was introduced by the IIEAWG but the BAD have requested it is removed as it duplicates the content of the reminder card.
- Guidance notes for the lead prescriber that were throughout the form have been collated into a single page and it is suggested that it is kept as a last page in the electronic version and a top page of the carbon copy pad.
- Feedback has been received that more information is needed regarding mental health side effects occurring at an unknown frequency and wording has been suggested to improve this.

The rationale for not incorporating some of the BAD proposed amendments are set out below:

- The BAD have suggested that the form is renamed as an initiation form ('Isotretinoin Initiation form'). There are concerns that this change in name alters the emphasis from a communication of risk to a clinical decision to start treatment and how this would be perceived by patients. It would be important to ensure a patient group is consulted on this change.
- Some tick boxes have been retained to evidence that each point has been discussed, however further patient engagement could be undertaken on this point.
- Blood testing, which is a long established practice and in the SmPC, was introduced into the Acknowledgement of Risk form by the IIEAWG but the BAD have requested it is removed from the Acknowledgement of Risk form. [The MHRA would not consider this at present as a full review of the evidence is required. However we have informed the BAD that we would welcome any research or data that would establish the requirement for testing liver function and serum lipids are not necessary.]
- Retained original warning from the first Acknowledgement of Risk form (before the implementation group changes) with instructions not to share medicines. The BAD asked for this to be removed as it this applies to all medicines and medical products. However, given the highly teratogenic nature of isotretinoin the MHRA believe it should not be removed.
- Information on circumstances where precautions should be taken with hormonal contraception was proposed by IIEAWG and the BAD have suggested removing the detail from the form as the information is available in their patient information. Due to

the teratogenic properties of isotretinoin, the MHRA believes it is important it is clear what can influence the effectiveness of the contraception in the form.

In addition, we have received minor suggestions for improvement from pharmacists and pharmacy professional bodies on the Pharmacist Checklist which have been included, noting that the BAD have also suggested removing the mental health reminder from the Pharmacist Checklist as this should have been covered by the Acknowledgement of Risk form.

It should be noted that there might be potential negative consequences after introducing a form that HCPs have become used to and is now embedded in practice. In addition, other than the BAD (clearly one of the main professional groups who use this form), no other stakeholder or group has raised significant issues with the current Acknowledgment of Risk form.

4.5.6 Reinstatement of MHRA guidance for remote pregnancy testing

4.5.6.1 The BAD concerns and proposal

The BAD request is as follows:

We would like to see the removal of the requirement for face-to-face follow-up appointments and the reinstatement of the MHRA guidance for remote pregnancy testing.

The BAD proposal

To change the requirement for face-to-face follow-ups, it would be necessary to allow pregnancy testing to be carried out by the patient remotely with results sent or shown to the HCP to inform the remote consultation. This was piloted during the pandemic and worked successfully.

4.5.6.2 Reinstatement of MHRA guidance for remote pregnancy testing.

All healthcare professionals should adhere to the pregnancy testing instructions within the SmPC for isotretinoin (section 4.4, special warnings and precautions for use) which are the regulatory requirements. Note that the SmPC instructions give some element of flexibility by referring to ‘local practice’:

Pregnancy testing
According to local practice, medically supervised pregnancy tests with a minimum sensitivity of 25 mIU/mL are recommended to be performed, as follows.
Prior to starting therapy
At least one month after the patient has started using contraception, and shortly (preferably a few days) prior to the first prescription, the patient should undergo a medically supervised pregnancy test. This test should ensure the patient is not pregnant when she starts treatment with isotretinoin.

Follow-up visits
Follow-up visits should be arranged at regular intervals, ideally monthly. The need for repeated medically supervised pregnancy tests every month should be determined according to local practice including consideration of the patient's sexual activity, recent menstrual history (abnormal menses, missed periods or amenorrhea) and method of contraception. Where indicated, follow-up pregnancy tests should be performed on the day of the prescribing visit or in the 3 days prior to the visit to the prescriber.

End of treatment
1 month after stopping treatment, women should undergo a final pregnancy test.

Prescribing and dispensing restrictions
For women of childbearing potential, the prescription duration of isotretinoin should ideally be limited to 30 days in order to support regular follow up, including pregnancy testing and monitoring. Ideally, pregnancy testing, issuing a prescription and dispensing of isotretinoin should occur on the same day. Dispensing of isotretinoin should occur within a maximum of 7 days of the prescription.
This monthly follow-up will allow ensuring that regular pregnancy testing and monitoring is performed and that the patient is not pregnant before receiving the next cycle of medication. For those patients that are considered by the prescriber to have compelling reasons to indicate that there is no risk of pregnancy, once stable on isotretinoin (after the first 1-3 months), the prescription duration may be for longer than 30 days (up to 12 weeks).

The IIAEWG did not provide specific advice on remote pregnancy testing. The MHRA guidance ‘Temporary advice for management of oral retinoid medicines during the COVID-19 pandemic’ was interim guidance during the pandemic for specialists and patients about oral isotretinoin, alitretinoin and acitretin, and the use of remote consultations for monitoring safety requirements. This was not intended to be permanent advice. The guidance was therefore out of date and withdrawn once the pandemic was over.

The Yellow Card data on pregnancies has been reviewed, summarised in Annex B, and there are no apparent increased trends in pregnancy during the use of remote pregnancy testing in the pandemic. It is worth noting the four pregnancies reported in 2023 are unrelated to the use of remote pregnancy testing with 1 patient having opted out of the prevention program and 1 patient reported to be on two methods on contraception, and the remaining two patients have limited detail.

There is a lack of data for private prescriptions and dispensing, as even if a private prescription is dispensed from a community pharmacy this will not be picked up by NHS Business Service Authority dispensing data. In addition, if the numbers are low it will be difficult to establish variations over time as numbers under 10 are not reported in detail.

The MHRA proposed signposting to the BAD clinical guidance on this topic aligned to the SmPC guidance. In addition, the MHRA will continue to closely monitor Yellow Card reports for an indication that remote pregnancy testing is leading to an increase in reported pregnancies, and also explore the use of other data sources.

4.5.7 Antimicrobial resistance

From their member surveys, the BAD are concerned that the new isotretinoin regulations are impacting on isotretinoin prescribing with a reduction in appropriate prescribing, and will lead to an increase in antibiotic usage and therefore antimicrobial resistance, due to reduced access to isotretinoin. However this is unlikely given that the new regulatory requirements did not change the therapeutic indication for isotretinoin. (The indication as stated in the SmPC is 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-bacterial and topical therapy.) In addition, the NICE Acne vulgaris: management guideline [NG198] advises prescribers to 'only continue a treatment option that includes an antibiotic (topical or oral) for more than 6 months in exceptional circumstances. Review at 3-monthly intervals, and stop the antibiotic as soon as possible.'

According to the NICE guideline, first-line treatment options include both topical or oral antibiotics (topical clindamycin or oral lymecycline or oral doxycycline).

First-line treatment options

Offer people with acne a 12-week course of 1 of the following first-line treatment options, taking account of the severity of their acne and the person's preferences, and after a discussion of the advantages and disadvantages of each option:

-a fixed combination of topical adapalene with topical benzoyl peroxide for any acne severity

-a fixed combination of topical tretinoin with topical clindamycin for any acne severity

-a fixed combination of topical benzoyl peroxide with topical clindamycin for mild to moderate acne

-a fixed combination of topical adapalene with topical benzoyl peroxide, together with either oral lymecycline or oral doxycycline for moderate to severe acne

-topical azelaic acid with either oral lymecycline or oral doxycycline for moderate to severe acne.

This guideline is similar to clinical medicine polices in other countries. For patients who cannot tolerate or have contraindications to oral lymecycline or oral doxycycline, prescribers are advised to consider replacing these medicines with trimethoprim or with an oral macrolide (for example, erythromycin). The prescriber is also advised to only continue a treatment option that includes an antibiotic (topical or oral) for more than 6 months in exceptional circumstances.

The BAD have supplied information on a local audit prior to the implementation of the isotretinoin recommendations. This shows that only between 18% to 25% of organisations are following the current NICE guidelines with the remaining prescribing antibiotics either as

a monotherapy, both oral and topical or noting dose discrepancies. The BAD acknowledge that this is clearly not in keeping with the recommendations and efforts have been made to improve this.

As a first-line treatment and given that the new regulatory requirements have not amended the indication for isotretinoin, there should be no changes to antibiotic prescribing for the initial treatment of acne vulgaris. However, it is possible that due to the likely increase in waiting times GPs may continue to prescribe antibiotics against guidelines.

4.5.8 Discussion

The CHM IEWG recommendations for regulatory change was introduced in October 2023, supported by guidance for implementation from the CHM IIAEWG.

Immediate issues were raised by the BAD (and independent dermatologists and private dermatology providers) regarding both the two prescribers and face to face consultations. Additionally, it was highlighted that many dermatology services were relying on Band 7 nurses to assess acne patients and prescribe isotretinoin. Consequently, in January 2024, the CHM reviewed IIAWG guidance and allowed for Band 7 nurses to prescribe isotretinoin with appropriate supervision, which seems to have mitigated this problem.

The BAD has provided data to support the issues they have raised. This includes references to new scientific literature, healthcare professional surveys, and suggestions to streamline the pathway (a shorter Acknowledgement of Risk form and changes to sexual function monitoring, mode of follow-up appointments and two prescribers) which are outlined below. The new scientific literature was limited by heterogeneity in study populations, sample sizes, comparison groups, and outcomes. It remains a huge challenge to identify data sources to effectively evaluate the impact of implementation, particularly in the under 18 age group, and which appropriately captures evidence since the recommendations were introduced. In addition, there are no electronic prescribing data for any of the four home nations (only individual trust or hospital system data). Furthermore, as the risk minimisation materials are in PDF format or paper based there is no central point where inputted information or number of forms is captured.

There is also no uniform baseline against which to measure impact, as services have been set up locally in such a wide variety of ways, with wide deviation also in clinical practice. This was supported by patient reports. Therefore the measures set out in the CHM IIAEWG report aimed to provide a standard which was deemed to be safe and acceptable (for example, in the types of health care professionals who could prescribe isotretinoin, the frequency and mode of follow-up, and guidance on how to assess and monitor for psychiatric and sexual side effects.)

There is an even more incomplete picture with regards to private prescribing. This is an increasingly used sector especially given the longstanding delays in dermatology outpatients. There are no clear means to establish whether health care professionals in this

sector are following the conditions of use as per the SmPC, nor is there any source of prescription data.

Qualitative feedback has been sought regularly in the past year from various professional bodies, stakeholders and all the devolved nations. From this feedback NHS services appear to have successfully implemented and embedded the new regulations following a period of initial disruption to reconfigure services. However, some services report an impact on capacity with increased waiting times (on top of longstanding, pre-existing delays for dermatology outpatient appointments, with some patients waiting months). Longer appointment times are reported as needed in order to go through the new risk ministration materials and appropriately counsel and monitor patients according to the revised requirements in the SmPC. While the BAD reports this reduces the number of new patients able to be seen within a clinic, this has also been reported as a positive change (feedback from Wales) as patients have had the time to discuss the risks and benefits fully with their doctor or HCP.

Section 5 outlines CHM advice on the following discussion topics.

4.5.8.1 Second healthcare professional

The introduction of two prescribers has been widely implemented within the NHS. However, it is unclear to the extent that private practitioners have complied with this regulatory requirement. This is the change that has caused the most disquiet with dermatologists. While there is no evidence of improved safety with two prescribers there is also no direct evidence of harm; however decreased capacity to see patients indirectly causes harm by possibly delaying access to treatment and potentially increasing the risk of scarring.

Many of the new studies identified were limited by small sample sizes (though some were large), unclear definitions of incident outcomes vs. pre-existing conditions, lack of information on dose, duration, and prior treatments, and potential biases, including confounding by indication, selection and channeling bias. While none of the newly published studies provide strong evidence supporting a causal association between isotretinoin and increased risks of neuropsychiatric outcomes, methodological shortcomings and conflicting findings limit their validity. The available published data in this area has limitations and is subject to bias, furthermore there was little specific evidence for under 18s.

The new data, on its own, is unlikely be sufficient to provide enough substantial evidence to reassure with respect to safety in under 18’s, particularly as the numbers of psychiatric and sexual adverse effects are potentially relatively low. This new data should be seen in the context of the evidence from patients who presented to the CHM as part of the IEWG Report. Collaborative Work with the University of Liverpool will help provide some additional data in certain areas together with the Post Authorisation Safety Study and Acne ID trial. However, these results will not be available for a considerable time and may not provide robust enough data to further characterise the risks.

Therefore, the CHM wanted a better understanding of who is prescribing isotretinoin and reassurance that acne services will undertake future audits if two prescribers is removed. The MHRA asked all dermatology services who prescribe isotretinoin to complete a survey regarding their service and to commit to undertake possible audits in the future. The CHM were reassured by the survey responses and were satisfied with the response rate to the survey of dermatology services.

4.5.8.2 Sexual Function side effects

There is limited new evidence since the publication of the IEWG report that adds to the knowledge about the nature and frequency of sexual function side effects.
It is therefore important that these risks are raised with patients at the start of treatment, that they are counselled and advised on what to do should any symptoms be experienced and that patients are encouraged to report any side effects experienced. This is in line with the recommendations of the IIAEWG which gave guidance on following SmPC requirement that "All patients should be asked about the presence of symptoms or signs of sexual dysfunction prior to starting treatment with isotretinoin, and monitored for the development of new sexual disorders during treatment."

There have also been reports that following the introduction of new risk minimisation measures, patients are now declining indicated treatment due to concerns about sexual function risk, (noting these risks are now being discussed so patients are fully informed).

The BAD have reported that the term "not known" in the SmPC and PIL is causing confusion and further guidance on what this means (possibly within the Acknowledgment of Risk form) would assist patients decision making. CHM advice on this was sought.

The MHRA also sought CHM advice on signposting stakeholders via an addendum on the IIAEWG report webpage to the BAD clinical guidance that would make this requirement as pragmatic as possible for clinicians, without losing the key function of checking for and monitoring of this adverse event.

4.5.8.3 Face to Face follow-up appointments

The recommendations on the mode of consultation were included as in the CHM IIAEWG report and do not form part of the SmPC or the PIL. While there is a perceived clinical advantage for face to face appointments, particularly on initiation of treatment, there has been feedback on the increased resource required for face to face follow up appointment and that patients should also have some choice in the mode of consultation. As this is not a regulatory requirement, the MHRA sought CHM advice on whether this could be highlighted in an addendum to the IIAEWG report which also recommends that best clinical practice should be followed, noting that the BAD was providing clinical guidance as the professional body.

4.5.8.4 Acknowledgement of Risk Form

The MHRA has received significant feedback primarily from the BAD over the increase in appointment time required to complete the Acknowledgement of Risk form. Therefore, the BAD and the MHRA have worked together to identify ways to streamline the form, building on learnings from its use in clinical practice, whilst ensuring that it meets the recommendations of the CHM IEWG report, and that patients were fully informed of risks prior to starting treatment. The MHRA sought CHM advice on the possible removal of some wording relating to blood testing and contraception, name of the form and tick boxes.

4.5.8.5 Remote Pregnancy Testing

During the pandemic remote pregnancy testing became normal and was an efficient method to check results, and there was temporary Covid-19 guidance on the MHRA website which has since been withdrawn. This was an interpretation of “medically supervised” according to local practice which forms part of the SmPC. How pregnancy testing was to be undertaken was not part of the IIAEWG report.

While there has not been an increase in Yellow Card reporting, the MHRA intends to continue to monitor the effect of the introduction of remote testing and suggests an addendum signposting to the BAD clinical guidance on this topic. The MHRA sought CHM advice on whether they should signpost to guidance that the BAD have offered to develop on how to undertake a medically supervised test (including remote testing), conforming to SmPC requirements.

5. CHM advice

The Commission on Human Medicines (CHM) considered and advised on issues associated with the implementation of the new regulatory requirements for isotretinoin at the CHM meetings in 2025.

The CHM noted:

i. Structural changes to clinical pathways in response to the IIAEWG report have been made by healthcare professionals, supported by the BAD, to improve the counselling of patients in order that they are fully informed of the benefits and risks of isotretinoin prior to starting treatment and to ensure consistent monitoring for any side effects.

ii. Ongoing concerns about private practice. Reports and evidence that some prescribing in the private sector does not adhere to the regulatory requirements and IIAEWG guidance. The lack of data sources from private providers limits understanding in this sector which is being used increasingly by patients to access treatments such as isotretinoin, due to the long-standing waiting times for dermatology appointments. There are cases where patients under the age of 18 were started on isotretinoin in the private sector without the agreement of a second prescriber or without completing the Acknowledgement of Risk form (including the Pregnancy Prevention Programme, which is required as the medication is highly teratogenic).

iii. Evidence that the requirement for two prescribers is leading to a reduced capacity and access. This includes questionnaire data from the BAD members and an NHS England impact assessment, both of which have limitations.

The purpose for the introduction of two prescribers in this population was for greater oversight in patients under the age of 18, to confirm that treatment was appropriate and that patients had the therapeutic indication of severe acne, resistant to adequate courses of standard therapies. The CHM noted that the data provided by the BAD illustrates very little disagreement between clinicians and the limited treatment options for severe acne, therefore it is not clear how much additional safety is gained from a second prescriber. Balanced against this, there is now evidence that the requirement for two prescribers is leading to a reduced capacity and access with further significant delays to treatment which could lead to harm through an increased risk of scarring and other associated consequences of acne.

Second Prescriber

The CHM discussed the regulatory requirement for two prescribers for patients under 18 years of age. The CHM heard about the many limitations of the current scientific evidence but noted that the direction and consistency of findings from the new evidence in terms of psychiatric adverse effects was reassuring. It was noted that it would be very difficult to develop a gold standard study that would provide robust evidence for either causality or frequency of psychiatric side effects. The CHM noted that one of the original purposes for the introduction of two prescribers in this population was to confirm that treatment was appropriate, and given the data provided by the BAD illustrates very little disagreement between clinicians and the limited treatment options for severe acne, it is not clear how much additional safety is gained from a second prescriber. Balanced against this, there is now evidence that the requirement for two prescribers is leading to a reduced capacity and access for young patients with further significant delays to treatment which could lead to harm through an increased risk of scarring and other associated consequences of acne. The CHM noted there needs to be a balance between the risk mitigations and access to treatment. However, the limited capture of clinical practice in the independent/private sector remains a concern. The CHM noted that structural changes to clinical pathways in response to the IIAEWG report have been made by healthcare professionals, supported by the BAD, to improve the counselling of patients in order that they are fully informed of the benefits and risks of isotretinoin prior to starting treatment and to ensure consistent monitoring for any side effects.

Therefore, the CHM considered that the requirement for two prescribers should be removed when alternative risk minimisation measures were in place that would ensure safe prescribing practices. The CHM recommended that this requirementin patients under 18 years of age should be removed contingent on both regular auditing of good clinical practice, led by the BAD, including in the independent/private sector (to provide reassurance that services were following the guidance); and the development of educational and guidance materials by BAD to address residual concerns and ensure patients are fully informed of the risks. Continued work by the BAD, in collaboration with the MHRA, would be important to generate new evidence, methods and metrics for monitoring.

The CHM further advised that there should be regular clinical audit to confirm that isotretinoin is being prescribed appropriately according to the licensed indication, including assessment of acne severity and previous treatments prior to initiation. The CHM requested that BAD should present evidence of compliance with this condition to reassure the CHM that the risk benefit balance of isotretinoin is maximised.

The CHM looked for reassurance that acne service will undertake future audits. Therefore, the MHRA asked all dermatology services who prescribe isotretinoin to complete a survey regarding their service and to commit to undertake possible audits in the future. The CHM

were reassured by the survey responses and were satisfied with the response rate to the survey of dermatology services.

The alternative risk mitigation measures to be introduced include:

1) Changes to the risk acknowledgment form for all patients:

a) to confirm that the patient understands the therapeutic indication of isotretinoin, and the prescriber to confirm that isotretinoin is clinically indicated for the patient and that there is no other appropriate effective treatment
b) to offer patients a second opinion
c) reference to watching a patient information video
d) the form will also be streamlined to fit two pages.

2) A clinical audit of risk minimisation measures overseen by the MHRA.

3) A patient information video produced by the BAD to explain the risks associated with isotretinoin treatment in another format, more easily accessible to some patients. The CHM asked to review the BAD script of the patient information video, and to highlight offering patients a second opinion in the BAD patient video.

The CHM asked to review the BAD script for the patient information video, which should emphasise the licensed indication of isotretinoin for severe forms of acne (such as nodular or conglobate acne or acne at risk of permanent scarring) that are resistant to adequate courses of standard therapy with systemic anti-bacterials and topical therapy. The CHM suggested that the video could include images of severe acne cases to reinforce this message.

Follow-up consultations guidance

The CHM has advised changes to the IIAEWG recommendations that follow-up consultations do not necessarily need to be in person (face to face) and could be remote if appropriate. It was emphasised that this should be discussed and agreed with the patient and should take into account the clinical assessment, the patient's needs and preferences and safeguarding considerations. Prescribers should be mindful of professional standards and best practice e.g. General Medical Council (GMC) guidance, guidance from professional bodies, and other relevant guidelines and local polices.

Remote pregnancy testing guidance

The CHM noted that the SmPC, as part of the Pregnancy Prevention Programme, specifies that: *'according to local practice, a medically supervised pregnancy test, with a minimum sensitivity of 25 mIU/mL, is recommended to be performed.'*
Pregnancy testing should be performed prior to starting therapy, at follow-up visits (which should be at regular intervals, ideally monthly), and at the end of treatment. Regarding follow-up visits, the SmPC clarifies 'the need for repeated medically supervised pregnancy tests every month should be determined according to local practice including consideration of the patient's sexual activity, recent menstrual history (abnormal menses, missed periods or amenorrhea) and method of contraception. Where indicated, follow-up pregnancy tests should be performed on the day of the prescribing visit or in the 3 days prior to the visit to the prescriber.' The CHM noted that during COVID such pregnancy tests were performed remotely and that there was no evidence from Yellow Card reporting to date, that this had led to any increase in exposure to isotretinoin in pregnancy. The CHM advised that remote pregnancy testing may be regarded as a medically supervised test with appropriate guidance and oversight, to ensure tests are performed correctly and safely. The CHM advised that this recommendation was conditional on regular clinical audits to monitor adherence to the requirements of the SmPC and would require the development of clinical guidance on remote pregnancy testing from the BAD. Routine pharmacovigilance, including through Yellow Card reporting will also monitor for any increase in reports of pregnancy following exposure in isotretinoin.

Sexual Function

Frequency of sexual dysfunction
The CHM discussed the description of frequency of sexual function side effects as unknown in the SmPC, Patient Information Leaflet and Acknowledgement of Risk form. The CHM advised that 'not known' is a regulatory term that is used when the incidence is not known. The CHM advised that there was insufficient evidence to change this, and that a frequency of 'not known' is a true reflection of the current state of knowledge, which should be explained clearly to patients.

Monitoring of sexual dysfunction
The CHM advised that patients should be asked about sexual function at follow up appointments, although by the third appointment, this may be brief (and could be aided by use of a questionnaire before the consultation). In addition, information on this topic should be contained in a patient information video to be developed by the BAD. CHM noted this monitoring was particularly important as the timeframe of onset of sexual function side effects is not known and has been reported to persist after treatment has completed.

The CHM strongly encouraged further research to better understand the association between isotretinoin and sexual dysfunction but acknowledged the challenges with collecting evidence regarding sexual function and the potential limitations of the evidence that may be generated in the near future. Patient reported outcomes/side effects at follow up appointments could be a possible means to obtain data on the risk of this potential side effect.

Risk minimisation materials changes

Acknowledgement of Risk form and Pharmacist checklist

The CHM agreed to the proposed revisions to the Acknowledgement of Risk form). The CHM advised that the name of the form should be retained as it reflects the purpose of the form; a list of risks that need to be acknowledged by the patient. The CHM agreed the information on blood tests should be removed (as this is not a risk per se, this information was not part of the original acknowledgement of risk form, and the requirement for blood testing is in the SmPC), but that the mental health reminder on the Pharmacist Checklist should be retained.

6. Next steps

An addendum to the IIAEWG report has been published highlighting revisions to IIAEWG guidance that:

- follow-up consultations do not necessarily need to be in person (face to face) and could be remote if appropriate,
- CHM advice that remote pregnancy testing may be regarded as a medically supervised test with appropriate guidance and oversight, to ensure tests are performed correctly and safely, and
- confirming that patients should be asked about sexual function at follow up appointments, although by the third appointment, this may be brief (and could be aided by use of a questionnaire before the consultation).

Since conclusion of the CHM review, the MHRA has been working to enact the recommendations. The MHRA will work with the BAD to engage with non-responders to the MHRA survey.

Further risk mitigation measures that will be introduced include a clinical audit of isotretinoin prescribing developed by the BAD and overseen by MHRA, and a new patient information video developed by the BAD, with advice received from the CHM on the script. The BAD clinical audit proforma has been developed with advice from the CHM. The MHRA will collaborate with the Care Quality Commission to incorporate the standards within clinical audit into their inspection methodology. CHM noted that the future clinical audit of the risk minimisation measures led by the BAD will be very important as a measure of adherence to the regulatory requirements and guidance. If there is evidence of poor practice, other measures will be considered by the CHM such as pharmacy registration.

The MHRA has requested Manufacturing Authorisation Holders (MAHs) for isotretinoin to remove the requirement for a second prescriber for the initiation of isotretinoin treatment for severe acne in patients under 18 years of age. This involves changes to the product information (SmPC, Patient Information Leaflet) and Risk Minimisation Materials with a revised Acknowledgement of Risk form introduced. The revised form is more streamlined, includes an additional question on seeking a second opinion, a question to confirm the patients understanding of the therapeutic indication, and reference to the patient information video.

A Drug Safety Update will communicate these changes to health care professionals in conjunction with this Public Assessment Report.[9]

The MHRA will continue to work with all stakeholders and review the effectiveness of the updated regulatory requirements for isotretinoin.

The MHRA will continue to monitor the safety of isotretinoin and will take further regulatory action if this is appropriate.

[9] Note that updates to follow-up consultations guidance, remote pregnancy testing guidance, and sexual function monitoring have been communicated to healthcare professionals in the Drug Safety Update (DSU) of 27 October 2025.

7. References

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8. Glossary of terms

Clinical Practice Research Datalink (CPRD)
CPRD is a real-world research service supporting retrospective and prospective public health and clinical studies. CPRD collects anonymised data from a network of GP practices across the UK.

Commission on Human Medicines
The Commission on Human Medicines (CHM) advises ministers on the safety, efficacy and quality of medicinal products.

Health Canada
A federal institution responsible for helping Canadians maintain and improve their health.

Incidence
The rate of new cases of a disease or other health outcome of interest occurring in a population over a period of time.

Indication
The disease or condition, or manifestation or symptoms thereof, for which the drug is approved. As well as whether the drug is indicated for the treatment, prevention, mitigation, cure, relief, or diagnosis of that disease or condition.

Marketing authorisation holder
The company or other legal entity that has the authorisation to market a medicine in the UK.

Medical Dictionary for Regulatory Activities (MedDRA)
The Medical Dictionary for Regulatory Activities (MedDRA) is an internationally used set of terms relating to medical conditions, medicines and medical devices.

National Institute for Health and Care Excellence
The National Institute for Health and Care Excellence (NICE) provides national guidance and advice to improve health and social care. Their role is to improve outcomes for people using the NHS and other public health social care services. They also provide clinical guidance on how to manage specific conditions in England.

NHS Business Services Authority
The NHS Business Services Authority is an Arm's Length Body of the Department of Health and Social Care, responsible for providing platforms and delivering services that support the priorities of the NHS, Government and local health economies.

Patient Information Leaflet
Medicine packs includes a Patient Information Leaflet (PIL), which provides information on using the medicine safely. PILs are based on the Summaries of Product Characteristics (SPCs) which are a description of a medicinal product's properties and the conditions attached to its use.

Prevalence
The proportion of individuals in a defined population that have a disease or other health outcomes of interest at either a specified point in time (known as point prevalence) or during a specified period of time (period prevalence).

Primary Care
Primary care services provide the first point of contact in the healthcare system, acting as the ‘front door’ of the NHS. Primary care includes general practice, community pharmacy, dental, and optometry (eye health) services.

Secondary Care
Secondary care services are those provided by medical specialists, who in general do not have the first contact with the patient.

Summary of Product Characteristics (SmPC)
Detailed information that accompanies every licensed medicine, listing its composition and characteristics and conditions attached to its use, which is available at: https://www.gov.uk/guidance/find-product-information-about-medicines

Therapeutic Goods Administration (TGA)
The TGA is Australia’s government authority responsible for evaluating, assessing and monitoring therapeutic goods which include medicines, medical devices and biologicals.

Yellow Card scheme
The MHRA’s scheme for healthcare professionals and members of the public to report suspected adverse reactions for a medicine or vaccine, as well as medical devices and other products.

9. Annexes

Annex A Review of published literature since the last CHM review

Studies evaluating the risk of sexual dysfunction

Studies identified by the BAD

Li et al. Sexual Dysfunction Following Retinoids: A Systematic Review. British Journal of Dermatology. 2024; 23;192(1):175-177. doi: 10.1093/bjd/ljae361.

This systematic review aimed to evaluate the evidence for a causal association between post-retinoid sexual dysfunction (PRSD) and retinoid exposure. Due to the heterogeneity of the study designs, a meta-analysis could not be conducted so no pooled measures of effect were calculated.

The review included 11 studies. 6 of the 11 studies reported results specifically for isotretinoin. 3 were single case reports (1 biological male, 1 biological female and 1 female-to-male transgender) reporting ejaculation failure, vaginal bleeding and dyspareunia. The authors identified several potential sources of bias including limited information on past medical history and unclear duration of follow-up.

Two case series reported results for isotretinoin. The Healy et al. study was assessed in the previous MHRA/CHM 2023 review. A cross-sectional study by Cunningham et al. was also assessed in the previous MHRA/CHM review.

The Kaplan-Marans et al. study used the US FDA adverse event reporting system and reported a proportional reporting ratio of 1.24, (1.03-1.45) for erectile dysfunction in 181 males. Potential sources of bias identified included unclear method of clinical assessment of sexual dysfunction, limited information on patient demographics and no country of origin specified.

A matched cohort study by Thang et al. conducted in the TriNetX US Collaborative Network found no significant differences in the risk of erectile dysfunction (adjusted risk ratio = 1.0, 95% CI; 0.55-1.8), sexual dysfunction (aRR = 0.74, 95% CI; 0.39-1.38, decreased libido (aRR = 1.0, 95% CI: 0.42-2.4) or PDE5 inhibitor use (aRR = 1.1, 95% CI: 0.62-1.9) when comparing isotretinoin-exposed males to those treated without systemic medications. The authors identified unclear duration and dosage of isotretinoin use as a potential source of bias.

Overall, the authors noted most included studies were case series, limited by small sample sizes, lacked comparator groups and were subject to confounding, selection and reporting biases.

The authors concluded that evidence supporting a causal association is conflicting and based on studies of poor quality. The authors also conclude that dermatologists and patients should be aware of the conflicting data regarding sexual dysfunction associated with systemic retinoid therapy. Routine screening for sexual side-effects during systemic retinoid therapy may be reasonable as patients are less likely to self-disclose sexual health concerns.

Epidemiological Assessor's comments:

The systematic review protocol was pre-registered on PROSPERO (CRD42023495820). The search strategy involved searching only two databases (MEDLINE and EMBASE) additional databases could have included Web of Science, so there is a risk some studies may not have been identified. Additionally, only two keywords were used in the search

criteria which included “sexual dysfunction” and “retinoids” and again some relevant studies may not have been captured by the literature search. A more comprehensive search strategy could have included additional keywords (e.g. isotretinoin, erectile dysfunction etc).

Two research team members evaluated eligibility criteria for all records and were blind to each other’s decisions. Similarly, two reviewers independently identified sources of biases and disagreements were resolved in discussion with a third team member. These are appropriate methods to minimise errors and subjectivity.

The JBI critical appraisal tool was used for the risk of bias assessment. The tool consists of a checklist by which studies can be evaluated including for risk of bias and it does not give any consideration to the relative importance of the different potential sources of bias. The biases identified were therefore described in a qualitative manner in a table presented in the paper. However, the assessment is brief and lacks detail. For example, one cross-sectional study by Kara Polat et al. was described as a “good quality study” with no further explanation given.

An assessment of potential publication bias was also not conducted but as it was not possible to perform a meta-analysis due to the heterogeneity across study designs this it to be expected.

Overall, whilst the review was carried out in line with best practise methodology, the underlying studies have limitations and show conflicting results.

Tan et al. Exploring the association between isotretinoin and sexual dysfunction: a comprehensive scoping review. Clinical and Experimental Dermatology 2024 49 (11); 1396–1404. doi.org/10.1093/ced/llae168.

The aim of this review was to evaluate the methodology and quality of studies investigating the association between isotretinoin and sexual dysfunction and to examine the definitions of sexual dysfunction used.

The study refers to the concerns over the potential treatment emergent adverse sexual effects of isotretinoin which led to the Commission on Human Medicines’ Isotretinoin Expert Working Group recommending that all patients be counselled about the possible risk of sexual dysfunction from isotretinoin. The authors state they have raised concerns about the foundation of the recommendation, citing issues such as the absence of evidence-grading and the selection biases in the manuscripts used to substantiate the report.

After screening, 46 human studies were identified, of which 39% were case reports or case series, 7% were pharmacovigilance reports and the remaining 54% were epidemiological studies.

11 studies used a prospective cohort design, the largest comprising 105 patients. 2 studies used a retrospective cohort design, the largest composed of 466 patients. The majority of studies were from Turkey (n=13, 28%), followed by the United States (n=9, 20%) and the UK (n=8, 17%).

The predominant dosage fell in the range 0.5-1.0 mg/kg/day as observed in 20 studies. In 12 studies, the dose was unspecified and in 6 studies, specific doses were mentioned without consideration of body weight. The most common treatment duration was 1-6 months but 11 studies did not specify the therapy duration.

The definition of sexual dysfunction was heterogeneous across studies and so the review authors derived 9 classifications. Hormonal and metabolic parameters were the focus of highest number of studies (n=16). Alterations in menstruation were documented in 8 studies and altered semen parameters in 9 studies.

The majority of studies reported either a beneficial or neutral effect on sexual function (n=25, 54%) with the remaining reporting a deleterious effect (n=21, 46%).

The review found evidence connecting isotretinoin to sexual dysfunction is very poor as a significant proportion of the studies were of low methodological quality. 41 out of 46 studies (89%) ranked in the second lowest Oxford EBM categories and these comprised case reports, case series, poor quality cohort or case-control studies. The highest Oxford EBM category of the analysed studies was 2b which was a prospective cohort study of 81 men where serum and semen parameters were analysed over a period of 6 months. The authors state the CHM review placed a disproportionate emphasis on stakeholder input, which falls within the lowest categories (4 & 5) of the Oxford Evidence-Based Medicine classification.

The authors highlight none of the studies reviewed indicated whether isotretinoin was ingested with food, which is important as the bioavailability varies among individuals because of its lipophilic properties. Additionally, duration of treatment was not disclosed in nearly a quarter of the studies. The authors also noted high heterogeneity in sexual dysfunction definitions across the studies.

The authors conclude there is insufficient evidence linking isotretinoin to sexual function. They state high quality studies including large prospective studies are needed together with a uniform definition of sexual dysfunction. Additionally, creating a precise definition and following an established structure for recording sexual history will promote uniformity among dermatologists ensuring they inquire about specific pertinent symptoms.

Epidemiological Assessor's comments:

The study was described as a scoping review and was not registered with PROSPERO as a scoping review is not part of its registration protocols. The authors have not clarified what is meant by a scoping review but is consistent with the style of a literature review.

PubMed and Google scholar were searched. Additional databases could have been searched so there is the risk some relevant studies may have been missed. The search terms used appear to be comprehensive. Reviews and meta-analyses were excluded from the search a priori, but their reference lists could have been searched to capture additional relevant studies.

Studies included in the review were assessed according to the methodological design, their quality in terms of the Oxford Evidence Based Medicine (EBM) scale and to investigate how sexual dysfunction was defined and classified. Guidance documents on the use of the Oxford EBM hierarchy state that it is designed as a short cut for time-constrained researcher to find the likely best evidence. The Oxford EBM also categorises studies according to the classical hierarchy of evidence, which places randomised controlled trials higher than observational studies. Alternative critical appraisal tools, such as the ROBINS-I tool, have shifted away from the classical hierarchy towards an assessment of the risk of potential bias across different domains and how the study may deviate from an ideal hypothetical pragmatic RCT or target trial.

The paper states methods and results sections were thoroughly reviewed by three investigates to select studies that met criteria; however, it is unclear how disagreements between the reviewers were resolved.

Of the 46 human studies included in the scoping review, 5 were published from 2021 onwards. These included 3 studies with outcomes outside the scope of this review (menstrual irregularities, ovarian reserve, and semen parameters) a poster abstract, and a query of an adverse event reporting system. As such, little new evidence is added by this scoping review.

Studies evaluating the risk of risk of neuropsychiatric conditions

Studies identified by the BAD

Kridin K, Ludwig RJ. Isotretinoin and the risk of psychiatric disturbances: A global study shedding new light on a debatable story. J Am Acad Dermatol. 2023 Feb;88(2):388-394. doi: 10.1016/j.jaad.2022.10.031.

Aims

The aim of this study was to evaluate the risk of a range of psychiatric outcomes among patients with acne treated with isotretinoin compared to oral antibiotics using a retrospective cohort design.

Methods

The study used the TriNetX Analytics network platform, which is a global federated health research network comprising anonymised electronic healthcare records (EHRs) from approximately 117.5 million patients from 86 healthcare organisation worldwide. The patient EHRs are derived from hospitals, primary care and specialty treatment providers covering a range of geographic locations and ethnicities.

The cohort comprised patients with a diagnostic code for acne and were then subdivided into two treatment groups. The first group consisted of patients treated with isotretinoin. The second group consisted of patients treated with oral antibiotics (doxycycline, minocycline, tetracycline, roxithromycin and azithromycin) but no prescription for isotretinoin. The index date was the date on which isotretinoin or first oral antibiotic was initiated.

The two treatment cohorts were propensity score matched for demographic variables (age, sex, race and ethnicity) comorbidities (smoking, obesity, diabetes mellitus, hypertension, hyperlipidaemia, ischaemic heart disease and chronic kidney disease) and socioeconomic determinants of health (ICD-10 codes “problems related to education and literacy”, “problems related to employment and unemployment” and “occupational exposure to risk factors”). Propensity score matching was conducted using a 1:1 matching nearest neighbour greedy algorithm with a caliper of 0.25 times the standard deviation.

A sensitivity analysis was also conducted to include only patients exposed to isotretinoin without prior exposure to oral antibiotics to elucidate the independent role exerted by isotretinoin and removing any potential residual confounding from previous oral antibiotic exposure.

The statistical methods included the Kaplan-Meier survival analysis and Cox proportional hazards regression model.

Outcomes

The outcomes included depression, major depressive disorder (MDD), suicidal ideation, suicide attempt, post-traumatic stress disorder (PTSD), anxiety, bipolar disorder, schizophrenia, adjustment disorder and all-cause mortality.

Results

In total, the cohort consisted of 151,416 patients with acne, with 75,708 treated with isotretinoin and 75,708 treated with oral antibiotics. Overall, 48.3% of the cohort were female and the mean (SD) age at initiation of isotretinoin was 21.7 (9.1) years and for oral antibiotics was 21.8 (9.3) years.

Table II of the paper presents the adjusted risk estimates for psychiatric outcomes of interest among patients with acne treated with isotretinoin compared to those treated by oral antibiotics.

Isotretinoin was associated with a lower risk of depression (HR, 0.90; 95% CI: 0.87-0.93; P<0.001), but a comparable risk of MDD (HR, 0.97; 95% CI: 0.92-1.03; P = 0.318). The risk of suicide attempt was comparable between the two treatment groups (HR, 0.97; 95% CI: 0.85-1.11; P = 0.663), whereas the risk of suicidal ideation was greater among the isotretinoin group (HR, 1.41; 95% CI: 1.32-1.50; P<0.001).

Isotretinoin was associated with decreased risk of PTSD (HR, 0.75; 95% CI: 0.68-0.82; P<0.001), anxiety (HR, 0.84; 95% CI: 0.82-0.87; P<0.001), bipolar disorder (HR, 0.65; 95% CI: 0.59- 0.72; P <0.001), schizophrenia (HR, 0.60; 95% CI: 0.48-0.76; P<0.001), and adjustment disorder (HR, 0.82; 95% CI: 0.77-0.87; P<0.001).

Table II. Risk of psychiatric outcomes among patients with acne managed by isotretinoin relative to those managed by oral antibiotics

	Isotretinoin			Oral antibiotics			Risk difference	Hazard ratio	
Disease	No. eligible participants*	No. Outcomes	Risk, %	No. eligible participants*	No. Outcomes	Risk, %	(95% confidence interval, %)	(95% confidence interval)	*P* value
Depression	67,865	5944	8.8	68,043	9197	13.5	−4.8 (−5.1, −4.4)	**0.90 (0.87-0.93)**	**<.001**
Major depressive disorder	73,658	2205	3.0	74,017	3405	4.6	−1.6 (−1.8,−1.4)	0.97 (0.92-1.03)	.318
Suicidal ideation	73,881	1919	2.6	74,471	1886	2.5	0.1 (−0.1, 0.2)	**1.41 (1.32-1.50)**	**<.001**
Suicidal attempt	75,356	353	0.5	75,429	510	0.7	−0.2 (−0.3, 0.1)	0.97 (0.85-1.11)	.663
Post-traumatic stress disorder	74,934	695	0.9	74,883	1399	1.9	−0.9 (−0.1, −0.8)	**0.75 (0.68-0.82)**	**<.001**
Anxiety	65,735	7426	11.3	65,639	12,448	19.0	−7.7 (−8.1, −7.3)	**0.84 (0.82-0.87)**	**<.001**
Bipolar disorder	74,887	569	0.8	74,663	1283	1.7	−1.0 (−1.1, −0.8)	**0.65 (0.59-0.72)**	**<.001**
Schizophrenia	75,603	100	0.1	75,553	248	0.3	−0.2 (−0.2, −0.1)	**0.60 (0.48-0.76)**	**<.001**
Adjustment disorder	73,688	1466	2.0	73,380	2648	3.6	−1.6 (−1.8, −1.5)	**0.82 (0.77-0.87)**	**<.001**

Significant values are in bold.
No., Number of.
*Patients who had the investigated outcome prior to the initiation of the drugs were excluded from the analysis.

The sensitivity analysis comparing patients exposed to isotretinoin (without prior exposure to oral antibiotics) with those treated with oral antibiotics (Table III) showed similar trends at the primary analyses, but the adjusted hazard ratios tended to be lower.

For the all-cause mortality endpoint, 117 (0.16%) deaths occurred in the isotretinoin cohort compared to 337 (0.45%) in the oral antibiotics cohort. The risk of all cause-mortality was significantly lower among those treated with isotretinoin (HR, 0.56, 95% CI: 0.45-0.69, P<0.001).

Table III. Sensitivity analysis evaluating the risk of psychiatric outcomes among patients with acne managed by isotretinoin (without prior oral antibiotics) relative to those managed by oral antibiotics

	Isotretinoin (without prior oral antibiotics)			Oral antibiotics			Risk difference	Hazard ratio	
Disease	No. eligible participants*	No. Outcomes	Risk, %	No. eligible participants*	No. Outcomes	Risk, %	(95% confidence interval, %)	(95% confidence interval)	*P* value
Depression	24,107	1361	5.6	23,408	2987	12.8	−7.1 (−7.6, −6.6)	**0.74 (0.69-0.79)**	**<.001**
Major depressive disorder	25,406	522	2.1	25,321	1104	4.4	−2.3 (−2.6, −2.0)	0.90 (0.81-1.00)	.056
Suicidal ideation	25,444	400	1.6	25,463	594	2.3	−0.8 (−1.0, −0.5)	**1.17 (1.03, 1.33)**	**.018**
Suicidal attempt	25,783	80	0.3	25,780	150	0.6	−0.3 (−0.4, −0.2)	0.92 (0.70-1.21)	.554
Post-traumatic stress disorder	25,707	143	0.6	25,596	464	1.8	−1.3 (−1.4, −1.1)	**0.58 (0.48-0.70)**	**<.001**
Anxiety	23,499	1871	8.0	22,628	4103	18.1	−10.2 (−10.8, −9.6)	**0.75 (0.71-0.80)**	**<.001**
Bipolar disorder	25,685	127	0.5	25,533	446	1.7	−1.3 (−1.4, −1.1)	**0.52 (0.42-0.63)**	**<.001**
Schizophrenia	25,841	27	0.1	25,821	95	0.4	−0.3 (−0.3, −0.2)	**0.55 (0.36-0.86)**	**.007**
Adjustment disorder	25,507	296	1.2	25,170	877	3.5	−2.3 (−2.6, −2.1)	**0.61 (0.54-0.70)**	**<.001**

Significant values are in bold.
No., Number of.
*Patients who had the investigated outcome prior to the initiation of the drugs were excluded from the analysis.

Authors' discussion

The authors identified several limitations including the under, over or mis-diagnosis of the outcomes of interest and residual confounding by unmeasured factors. The TriNetX database represents patients who had medical encounters with healthcare systems and might overlook patients with low access to healthcare facilities. The study also did not account for drug dosage and lacked information on the severity of acne and psychiatric conditions. Additionally there confounding my indication cannot be ruled out if acne is prescribed to patients with more severe acne.

Overall, the study found a decreased risk of depression, PTSD, anxiety, bipolar disorder, schizophrenia and adjustment disorder in patients prescribed isotretinoin compared to those prescribed oral antibiotics, but an increased risk of suicidal ideation. There was no difference in the risk of suicide attempt or major depressive disorder when comparing the two exposure cohorts.

Epidemiological Assessor's comments:

The study used data from the TriNetX federated data network, which includes EHR data from multiple countries. It is unclear which countries were included in the study conducted and what the characteristics of the underlying population are. It is noted from table I that approximately 71% of the cohort are described as "not Hispanic or Latino" and the remaining 29% as "Hispanic or Latino", which again raises questions regarding the underlying population.

At the present time, approximately 30 million patients from North America and 6.5 million from Eastern Asia make up a high proportion of the TriNetX network. The healthcare organisations which contribute to the network in the US are mainly large academic centres, where patients may have different characteristics compared with other healthcare settings and providers. However, it is unclear how the underlying characteristics of the target population from these mostly academic centres would differ from other healthcare centres and so may not entirely representative of the US population. Furthermore, it is unclear whether combining EHR data, which included patients on private or public health insurance plans is appropriate due to differences in socioeconomic status and the underlying risk of the outcomes of interest. Higher rates of suicidal ideation and suicide attempt have been reported among public insurance programmes such as Medicaid

compared to those with private health insurance, although these disparities have narrowed since the Affordable Care Act (Cho et al, 2024). There could also be differences between the insurance plans in the coverage of acne treatments.

The paper lacks detail on certain aspects of the study design. The study period has not been defined so it is not known when the start and end of follow-up was. The censoring strategy has not been described, so it is also unclear when patient follow-up was censored. The index date was defined as the date of the first isotretinoin or first oral antibiotic prescription, which is appropriate, but it is unclear whether a minimum amount of prior follow-up prior to the first prescription was imposed as part of the eligibility criteria.

Regarding the outcomes of interest, it is unclear whether the outcomes are incident (newly diagnosed following medication exposure) or prevalent (pre-existing before initiation of acne treatment). The presence of prevalent patients with pre-existing outcomes would lead to confounding. It is also unclear how long patients were followed up for and the risk window for assessing outcomes was also not defined.

It is also unclear from the paper whether the TriNetX data network or individual databases contributing to it have validated the outcome of suicidal ideation, which is likely to be under-reported as not all patients may seek medical assistance or report it to a healthcare professional. The under-recording is likely to be non-differential between the exposure groups, which would bias the effect estimates towards the null.

Table 1 shows the prevalence of comorbidities is low in both cohorts and not greater than 4% for any of the comorbidities measured, which is to be expected given the young patient population (mean age of approximately 22 years). Propensity score matching was used to deal with confounding, however there is still the potential for residual confounding by other unmeasured comorbidities which are associated with acne including peptic ulcers, IBS, gastroenteritis, gastro-oesophageal reflex disease (GORD) and constipation (Chen et al, 2025). Whilst adverse socioeconomic determinants of health based on two ICD-10 codes were included in the propensity score models, these codes may not be sufficiently granular to fully capture socioeconomic status and therefore there could still be residual confounding by this variable. It is also unclear how widely used these codes are in clinical practice. In the results tables, the authors have omitted the unadjusted hazard ratios and only presented the adjusted results following propensity score matching, so it is not possible to assess the extent of confounding.

The authors note that isotretinoin is typically used as an acne treatment if oral antibiotics have failed. Patients initiating isotretinoin treatment could therefore have more severe acne and therefore be at a greater risk of psychiatric events, leading to confounding by acne severity. The authors conducted a sensitivity analysis to account for this by excluding patients with prior oral antibiotic exposure in the isotretinoin group, which produced similar results as the primary analysis but with attenuated risk estimates.

The results for the all-cause mortality endpoint suggest the isotretinoin cohort had a significantly lower risk of all-cause mortality compared with the oral antibiotic cohort. Is it unclear and why this might be but raises concerns that the two cohorts may not be truly comparable. If the risk of all-cause mortality was significantly then then it is perhaps unsurprising the risk of the other outcomes was broadly significantly lower as well.

Overall, whilst the results broadly suggest isotretinoin is associated with a decreased risk of psychiatric outcomes with the exception of suicidal ideation, it is difficult to determine whether the outcomes were based on prevalent or incident cases.

References:

Gastrointestinal comorbidities in patients with acne vulgaris: A population-based retrospective study. Yu-Wen Chen, Chun-Ying Wu, MD, Yi-Ju Chen, MD.

Cho A, Lee K. Association between insurance type and suicide-related behavior among US adults: The impact of the Affordable Care Act. Psychiatry Research 2024: 333; 115714. doi: 10.1016/j.psychres.2024.115714.

Paljarvi T, McPherson T, Luciano S, Herttua K, Fazel S. Isotretinoin and adverse neuropsychiatric outcomes: retrospective cohort study using routine data. British Journal of Dermatology. 2022 Jul;187(1):64-72. doi: 10.1111/bjd.21049.

Aims

The aim of this study was to establish and quantify the association between isotretinoin use for acne and 1-year incident neuropsychiatric adverse events.

Methods

The study used the TriNetX Analytics network platform, which is a global federated health research network comprising anonymised electronic healthcare records (EHRs) from 56 healthcare organisations mainly in the USA (91% of patients in the USA and 9% in Europe, Latin America and Asia-Pacific) at the time the study was conducted.

The TriNetX network included over 12.3 million patients aged 12-27 years between 2013 and 2019. Patients were eligible for inclusion in the study if they aged 12-27 years at the prescription index date, had a diagnosis of acne, did not have a diagnosis of neoplasms and were alive for the 12-month period following the index prescription. The inclusion and exclusion criteria were imposed, the isotretinoin-exposed cohort comprised 30,866 patients.

Three comparator cohorts were derived:

1. Oral antibiotic exposed (erythromycins, macrolides or tetracyclines) but unexposed to isotretinoin: n = 44,748.
2. Topical anti-acne exposed (unexposed to isotretinoin or oral antibiotics): n = 108,367.
3. Anti-acne unexposed (unexposed to isotretinoin, topical anti-acne medicines or selected oral antibiotics): n = 78,666.

For isotretinoin, oral antibiotics and topical anti-acne agents, the first dispensed prescription in was used as the index prescription; whereas for the third control cohort the first healthcare visit due to acne was used.

The isotretinoin-exposed cohort was propensity score matched with the three comparator cohorts according to type of acne, comorbidities and history of mental ill-health. Propensity score matching was conducted using the TriNetX built-in algorithm based on a 1:1 nearest neighbour matching with a caliper of 0.1 SDs.

Cohorts were balanced at baseline for the following covariates: age at index prescription or event; sex; ethnicity/race; mental and behavioural disorders because of psychoactive substance use; schizophrenia, schizotypal, delusional and other non-mood psychotic disorders; mood (affective) disorders; anxiety, dissociative, stress-related, somatoform and other nonpsychotic mental disorders; sleep disorders not because of a substance or known physiological condition; disorders of adult personality and behaviour; behavioural and emotional disorders with onset usually occurring in childhood and adolescence; sleep disorders; vasomotor and allergic rhinitis; asthma; dermatitis and

eczema; acne vulgaris; acne conglobata; other acne; unspecified acne; suicidal ideations; suicide attempt; intentional self-harm; and dispensed prescriptions for sedatives and hypnotics; antidepressants; antipsychotics; and glucocorticoids. Patients in the isotretinoin cohort were successfully matched with patients in the oral anti-biotics cohort (92%, 28398/30866), in the topical anti-acne agents cohort (99%, 30 435/30 866) and in the acne control cohort without dispensed prescriptions for the selected acne medications (92%, 28 417/30 866).

Outcomes

The outcomes of interest comprised a composite 12-month incident neuropsychiatric diagnoses (psychotic disorders; mood disorders; anxiety, dissociative, stress-related, somatoform and other nonpsychotic mental disorders; adult personality and behaviour disorders; behavioural and emotional disorders with onset usually occurring in childhood and adolescence; sleep disorders; and nonfatal self-harm, which also included events of undetermined intent. The listed diagnoses were also included as individual outcomes.

Secondary outcomes included 12-month incident dispensed prescriptions for psychotropic medicines, including sedatives and hypnotics; antidepressants; and antipsychotics as proxies for clinically important neuropsychiatric outcomes requiring treatment.

A 14-day washout period after the index prescription was used for measuring outcomes to reduce bias from conditions already present at the time of the index prescription.

Results

The OR for any incident neuropsychiatric outcomes in patients exposed to isotretinoin was 1.06 (95% CI 0.97–1.16) compared with patients with an acne diagnosis but who did not have dispensed prescriptions for any of the selected acne medication (Table 1); 0.94 (95% CI 0.87–1.02) compared with patients using topical anti-acne medicines (Table 2); and 0.80 (95% CI 0.74–0.87) compared with patients on oral antibiotics (Table 3).

Compared with patients with acne who unexposed to any of the acne medications, patients in the isotretinoin cohort had increased odds for incident mood disorders, anxiety disorders and sleep disorders (Table 1). The strongest associations were observed for incident prescriptions for psychotropic medicines, such as for antidepressants (OR 1.83, 95% CI 1.63–2.05). An association was also observed for symptoms involving emotional state (OR 1.40, 95% CI 1.15–1.72).

Compared with patients with acne using topical anti-acne agents, patients in the isotretinoin cohort had increased odds for incident prescriptions for antidepressants (OR 1.16, 95% CI 1.05–1.28) and for symptoms involving emotional state (OR 1.21, 95% CI 1.10–1.45), but all other ORs were not statistically significant, and most were close to a null association (Table 2).

When compared with patients in the oral antibiotics cohort, the patients in the isotretinoin cohort had decreased odds for incident neuropsychiatric outcomes (OR 0.80, 95% CI 0.74–0.87), and this applied to all neuropsychiatric outcomes except for psychotic disorders and symptoms involving emotional state with statistically nonsignificant ORs (Table 3). The decreased odds were statistically significant for mood disorders, anxiety disorders, behavioural disorders and incident prescriptions for psychotropic medicines. There was no clear association for nonfatal self-harm (OR 0.85, 95% CI 0.66–1.11).

Table 1 One-year incidence of neuropsychiatric outcomes among patients with acne exposed to isotretinoin compared with patients with acne who were not exposed to isotretinoin, oral antibiotics for acne or topical anti-acne agents during follow-up[a]

Outcomes	Isotretinoin (n = 28 417)			No selected anti-acne medication[b] (n = 28 417)			Odds ratio	95% CI
	Patients, total, n	Patients with incident outcome, n	IR/1000	Patients, total, n	Patients with incident outcome, n	IR/1000		
Any neuropsychiatric outcome	23 536	1064	45	23 438	998	42	1·06	0·97–1·16
Psychotic disorders	28 357	23	1	28 364	19	1	1·21	0·66–2·22
Mood disorders	26 447	600	23	26 608	536	20	**1·13**	1·00–1·27
Anxiety disorders	25 689	771	30	25 978	692	27	**1·13**	1·02–1·25
Personality disorders	28 070	53	2	28 106	61	2	0·87	0·60–1·26
Behavioural disorders	26 403	254	10	26 585	277	10	0·92	0·78–1·09
Sleep disorders	27 440	317	11	27 507	268	10	**1·19**	1·10–1·40
Self-harm, nonfatal	28 067	100	3	28 061	80	3	1·25	0·93–1·68
Dispensed prescriptions								
Sedatives and hypnotics	26 515	591	22	26 607	415	15	**1·44**	1·27–1·63
Antidepressants	25 604	815	32	25 753	455	18	**1·83**	1·63–2·05
Antipsychotics	27 857	161	6	27 892	106	4	**1·52**	1·19–1·95
Physical symptoms[c]	19 593	3081	157	20 287	1720	85	**2·01**	1·89–2·14
Symptoms involving emotional state[d]	27 760	226	8	27 858	162	6	**1·40**	1·15–1·72
Inpatient visits[e]	28 417	610	n/a	28 417	401	n/a	**1·53**	1·35–1·74
Emergency visits[e]	28 417	1838	n/a	28 417	1360	n/a	**1·38**	1·28–1·48

CI, confidence interval; IR, incidence rate per 1000 person-years; n/a, not applicable. [a]Patients aged 12–27 years at index prescription (isotretinoin) or index visit (acne control group) in 2013– 2019 after propensity score matching for all covariates. Oral antibiotics: erythromycins(macrolides) or tetracyclines. Results in bold are significant. [b]Healthcare contact during which a diagnosis for acne was recorded. [c]Physical symptoms of common isotretinoin side-effects, such as headache, nausea and vomiting, dry mouth, conjunctivitis, pain, cheilitis and fatigue. [d]Symptoms and signs involving emotional state, including various diagnoses for agitation and aggression. [e]Including patients with visits before index prescription (before start of follow-up).

Table 2 One-year incidence of neuropsychiatric outcomes among patients with acne exposed to isotretinoin compared with patients with dispensed prescriptions for topical anti-acne agents who were not exposed to isotretinoin or oral antibiotics for acne during follow-up[a]

Outcomes	Isotretinoin (n = 30 435)			Topical anti-acne agents[b] (n = 30 435)			Odds ratio	95% CI
	Patients, total, n	Patients with incident outcome, n	IR/1000	Patients, total, n	Patients with incident outcome, n	IR/1000		
Any neuropsychiatric outcome	24 977	1172	47	24 596	1220	50	0·94	0·87–1·02
Psychotic disorders	30 372	23	1	30 355	23	1	1·00	0·56–1·78
Mood disorders	28 258	688	24	28 278	724	26	0·95	0·85–1·06
Anxiety disorders	27 362	862	31	27 412	942	34	0·91	0·83–1·00
Personality disorders	30 035	60	2	30 030	80	3	0·75	0·54–1·05
Behavioural disorders	28 251	285	10	28 403	324	11	0·88	0·75–1·04
Sleep disorders	29 286	359	12	29 299	326	11	1·10	0·95–1·28
Self-harm, nonfatal	30 034	118	4	29 992	97	3	1·22	0·93–1·59
Dispensed prescriptions								
Sedatives and hypnotics	27 967	635	23	27 895	639	23	0·99	0·89–1·11
Antidepressants	26 774	851	32	26 766	738	27	**1·16**	1·05–1·28
Antipsychotics	29 703	181	6	29 726	162	5	1·12	0·90–1·38
Physical symptoms[c]	20 566	3263	159	20 646	1922	93	**1·84**	1·73–1·95
Symptoms involving emotional state[d]	29 690	260	9	29 665	215	7	**1·21**	1·10–1·45
Inpatient visits[e]	30 435	669	n/a	30 435	705	n/a	0·95	0·85–1·05
Emergency visits[e]	30 435	2037	n/a	30 435	2007	n/a	1·02	0·95–1·08

CI, confidence interval; IR, incidence rate per 1000 person-years; n/a, not applicable. [a]Patients aged 12–27 years at index prescription in 2013–2019 after propensity score matching for all covariates. Oral antibiotics: erythromycins(macrolides) or tetracyclines. Results in bold are significant. [b]Topical anti-acne agents, such as topical antibiotic preparations, tretinoin and benzoyl peroxide. [c]Physical symptoms of common isotretinoin side-effects, such as headache, nausea and vomiting, dry mouth, conjunctivitis, pain, cheilitis and fatigue. [d]Symptoms and signs involving emotional state, including various diagnoses for agitation and aggression. [e]Including patients with visits before index prescription (before start of follow-up).

Table 3 One-year incidence of neuropsychiatric outcomes among patients with acne exposed to isotretinoin compared with patients with dispensed prescriptions for oral antibiotics for acne who were not exposed to isotretinoin during follow-up[a]

Outcomes	Isotretinoin (n = 28 398)			Oral antibiotics[b] (n = 28 398)			Odds ratio	95% CI
	Patients, total, n	Patients with incident outcome, n	IR/ 1000	Patients, total, n	Patients with incident outcome, n	IR/ 1000		
Any neuropsychiatric outcome	22 974	1091	47	22 756	1332	58	**0·80**	0·74–0·87
Psychotic disorders	28 334	23	1	28 317	21	1	1·09	0·61–1·98
Mood disorders	26 220	654	25	26 232	828	31	**0·78**	0·71–0·87
Anxiety disorders	25 341	822	32	25 370	1028	40	**0·79**	0·72–0·87
Personality disorders	28 003	61	2	28 018	82	3	0·74	0·53–1·04
Behavioural disorders	26 221	263	10	26 340	320	12	**0·82**	0·70–0·97
Sleep disorders	27 256	340	12	27 267	378	14	**0·90**	0·77–1·04
Self-harm, nonfatal	28 003	106	4	27 997	124	4	**0·85**	0·66–1·11
Dispensed prescriptions								
Sedatives and hypnotics	26 025	610	23	26 127	694	26	**0·88**	0·79–0·98
Antidepressants	24 757	801	32	24 842	889	35	0·90	0·82–0·99
Antipsychotics	27 676	172	6	27 708	239	9	**0·72**	0·59–0·87
Physical symptoms[c]	18 899	3033	160	18 386	2068	112	**1·51**	1·42–1·60
Symptoms involving emotional state[d]	27 659	244	9	27 657	218	8	1·12	0·93–1·35
Inpatient visits[e]	28 398	650	n/a	28 398	804	n/a	**0·80**	0·72–0·89
Emergency visits[e]	28 398	1956	n/a	28 398	2359	n/a	**0·82**	0·77–0·87

CI, confidence interval; IR, incidence rate per 1000 person-years; n/a, not applicable. [a]Patients aged 12–27 years at index prescription in 2013–2019 after propensity score matching for all covariates. Results in bold are significant. [b]Oral antibiotics: erythromycins(macrolides) or tetracyclines. [c]Physical symptoms of common isotretinoin side-effects, such as headache, nausea and vomiting, dry mouth, conjunctivitis, pain, cheilitis and fatigue. [d]Symptoms and signs involving emotional state, including various diagnoses for agitation and aggression. [e]Including patients with visits before index prescription (before start of follow-up).

Authors' conclusions

A consistent association was observed between increasing acne severity as indicated by anti-acne treatment options and incidence of adverse neuropsychiatric outcomes, but the findings showed that isotretinoin exposure did not add to the risk of neuropsychiatric adverse outcomes over and above what was associated with oral antibiotics. Instead, it was observed that isotretinoin was associated with reduced incidence of anxiety, depression, sleep problems, nonfatal self-harm and prescriptions for psychotropic medicines when compared with patients with acne who were propensity score matched and prescribed oral antibiotics. Isotretinoin appeared to mitigate the excess neuropsychiatric risk associated with recalcitrant moderate-to-severe acne.

Epidemiological Assessor's comments:

This was a large study which included relatively large numbers of patients prescribed isotretinoin and evaluated the risk of several neuropsychiatric outcomes.

The study attempted to overcome the limitations of other studies by indirectly controlling for acne severity with the use of different comparator groups with the results suggesting a reduced risk of neuropsychiatric outcomes over 1-year of follow-up in the isotretinoin cohort compared to the propensity score matched oral antibiotic cohort. However, there is the potential for misclassification of both exposures and outcomes occurring before or after the index date if patients received healthcare from organisations which do not contribute data to the TriNetX network as noted by the authors. This misclassification could therefore bias the effect estimates.

The authors note that isotretinoin-exposed cohort had a slightly higher incidence of symptoms involving emotional state, which is a diagnostically heterogeneous and non-specific group of mental health symptoms. The authors state there is the potential for a detection bias if there is increased awareness of potential isotretinoin-induced side-effects or increased healthcare contact due to isotretinoin blood monitoring requirements. This

detection bias would bias the effect estimates away from the null due to these symptoms being over-estimated in the isotretinoin-exposed cohort.

The authors identified relevant limitations including a lack of information on the duration of treatment and treatment adherence, which is common to EHR database research. They also identify that there may be a delay in patients seeking healthcare for neuropsychiatric symptoms, especially if mild, which can obscure the temporal sequence of events. A 14-day washout period after the index prescription was used to overcome potential delays bias from conditions that were already present at the time of the index prescription which is a reasonable design feature to minimise the impact of delayed diagnoses.

As has been identified in the assessment of the Kridin et al study, which also used the TriNetX data, the healthcare organisations included whilst large may not be representative of all healthcare organisations in those jurisdictions and therefore there could be differences in patient characteristics, data quality and recording and isotretinoin prescribing preferences across organisations which may affect the results.

Overall, this was a large and well conducted observational study. The primary limitation is the lack of information on whether the healthcare organisations included are representative of the patient population.

Rajput I, Anjankar V P. Side Effects of Treating Acne Vulgaris With Isotretinoin: A Systematic Review. Cureus. 2024 16(3): e55946. doi:10.7759/cureus.55946.

This systematic review aimed to provide an overview of the side effects linked to isotretinoin treatment for acne vulgaris. The review considered several side-effects including psychiatric, but not sexual dysfunction. No meta-analysis was conducted.

The review included 38 studies, however no tables were presented summarising the studies in terms of the design, outcomes and results.

The review reported depression symptoms in acne patients were reduced as a result of isotretinoin treatment and there no strong evidence to suggest it increased the risk of newly diagnosed depression, other psychological conditions, or suicidal ideation in patients who were not already suffering from a mental health condition. The review also reported the risk of mood disorders, such as suicidal thoughts, increases in bipolar patients taking isotretinoin. No quantitative data was presented as part of the review.

The authors conclude that age among other variables can affect the frequency and intensity of adverse reactions and monitoring is essential.

Epidemiological Assessor's comments:

Overall, the paper is lacking detail in many areas described below and so could be considered more as a literature review rather than a systematic review.

PubMed, Cureus and other open-access journal articles were searched for studies. Additional databases could have included EMBASE and Web of Science, so there is the potential some relevant studies were missed. The search strategy describes combinations of keywords like "treating acne vulgaris with isotretinoin" and "side effects of isotretinoin" were used, however the lack of detail makes it difficult to determine how comprehensive the search strategy was and if relevant keywords were excluded. To identify potential additional records from other sources, a literature search was conducted to locate case-

control studies and meta-analyses. Again, the lack of detail on what the other sources comprised and why other study designs including cohort studies were not considered is unclear and so some relevant studies may have been excluded.

No detail was provided on how data was extracted from identified studies, the number of reviewers and how disagreements on data extraction and sources of bias were resolved. There does not appear to be any assessment of potential publication bias.

Given the limitations identified and the structure of the review, little new evidence is added.

Tan et al. Risk of Suicide and Psychiatric Disorders Among Isotretinoin Users: A Meta-Analysis. JAMA Dermatology. 2024;160(1):54–62. doi:10.1001/jamadermatol.2023.4579

Aim

This meta-analysis aimed to clarify the absolute and relative risk and risk factors associated with suicide and psychiatric disorder among isotretinoin users. The results presented in this summary only include those quantifying the relative risk. The results for the absolute risks can be found in the original paper.

Methods

The meta-analysis follows an a priori systematic review protocol registered with PROSPERO (CRD42023388463) and is reported in accordance with PRISMA guidelines. Four databases (PubMed, Embase, Web of Science and Scopus) were searched from inception until 24/01/2023. The bibliographies of included articles and relevant reviews or journals were also manually searched. Two authors independently screened for eligible studies which included randomised clinical trials and observational studies that reported the absolute risk and risk factors for psychiatric disorders and suicide among patients with acne taking oral isotretinoin, and the relative risk of these disorders among patients taking oral isotretinoin compared with control participants not treated with isotretinoin. The risk of bias for each study was assessed using the Newcastle-Ottawa Scale (NOS) since all included studies were observational. Studies were graded as having high (<5 stars), moderate (5-7 stars) or low (≥8 stars) risk of bias. The GRADE system was used to evaluate the quality of pooled evidence at the outcome level. Publication bias was assessed via visual inspection of funnel plot asymmetry, Egger bias, or trim-and-fill method, as appropriate.

Results

A total of 25 observational studies were included in the review and 24 studies were eligible for inclusion in the meta-analyses. Among the included studies, participants' average age ranged from 16 to 38 years, and distribution by sex ranged from 0% to 100% male.

After adjustment for age, there was no association between isotretinoin use and suicide attempt during treatment, and at 6 months and 1 year following treatment (Figure 4). Isotretinoin users were less likely than nonusers to attempt suicide at 2, 3, and 4 years. No association was found between isotretinoin use and suicide attempt at 5 and 10 years.

Isotretinoin users were not at higher risk of all psychiatric disorders (pooled RR, 1.08; 95% CI, 0.99-1.19; I^2 = 0%; 4 studies), depression (pooled RR, 1.46; 95% CI, 0.55-3.87; I^2 = 80%; 2 studies), anxiety (pooled RR, 0.97; 95% CI, 0.73-1.30; I^2 = 97%; 2 studies), psychotic disorders (pooled RR, 0.80; 95% CI, 0.41-1.58; I^2 = 78%; 2 studies), and sleep disorders (pooled RR, 1.61; 95% CI, 0.89-

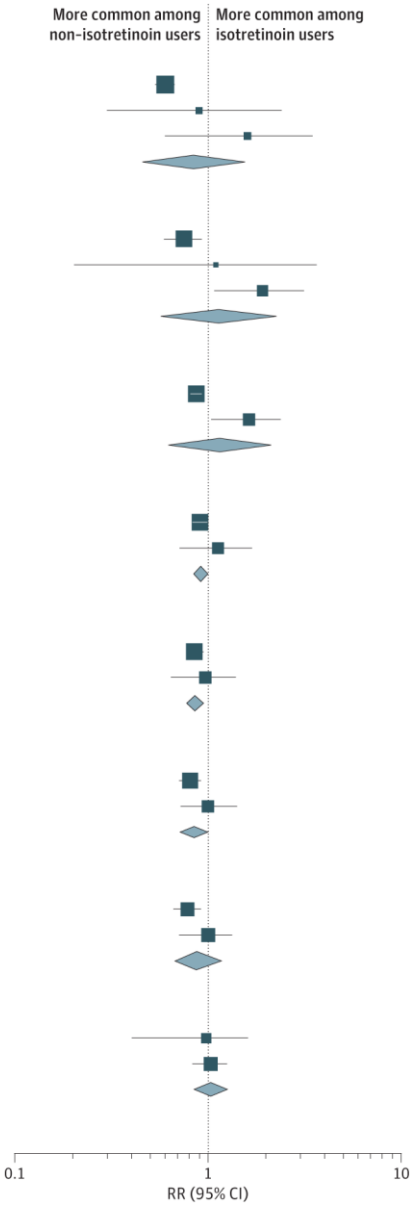
2.93; *I*2 = 98%; 2 studies) at 1 year following treatment. There were insufficient studies to assess publication bias.

Authors conclusions

The authors concluded that, at a population level, isotretinoin users do not have increased risk of suicide or psychiatric conditions. However, they suggest clinicians should continue to monitor patients for signs of mental distress during isotretinoin treatment.

Figure 4. Random-Effects Meta-Analyses of the Association Between Isotretinoin Use and Relative Risk of Suicide Attempt During Treatment and at 6 Months and 1, 2, 3, 4, 5, and 10 Years Following Treatment

Study	logRR (SE)	RR (95% CI)
Suicide attempt during treatment		
Droitcourt et al,[9] 2019	−0.51 (0.06)	0.60 (0.53-0.67)
Jick et al,[34] 2000	−0.11 (0.53)	0.90 (0.30-2.40)
Sundström et al,[23] 2010	0.48 (0.45)	1.61 (0.60-3.49)
Random-effects model		0.84 (0.45-1.56)
Heterogeneity: I^2 = 62%, τ^2 = 0.1840, P = .07		
Suicide attempt 6 mo following treatment		
Droitcourt et al,[9] 2019	−0.29 (0.12)	0.75 (0.59-0.93)
Jick et al,[34] 2000	0.10 (0.74)	1.10 (0.20-3.70)
Sundström et al,[23] 2010	0.66 (0.28)	1.93 (1.08-3.18)
Random-effects model		1.14 (0.57-2.29)
Heterogeneity: I^2 = 80%, τ^2 = 0.2578, P = .006		
Suicide attempt 1 y following treatment		
Droitcourt et al,[9] 2019	−0.14 (0.04)	0.87 (0.81-0.93)
Sundström et al,[23] 2010	0.50 (0.21)	1.64 (1.04-2.40)
Random-effects model		1.15 (0.62-2.14)
Heterogeneity: I^2 = 88%, τ^2 = 0.1776, P = .003		
Suicide attempt 2 y following treatment		
Droitcourt et al,[9] 2019	−0.09 (0.04)	0.91 (0.83-0.99)
Sundström et al,[23] 2010	0.12 (0.22)	1.13 (0.71-1.70)
Random-effects model		0.92 (0.84-1.00)
Heterogeneity: I^2 = 0%, τ^2 = 0, P = .34		
Suicide attempt 3 y following treatment		
Droitcourt et al,[9] 2019	−0.16 (0.05)	0.85 (0.77-0.95)
Sundström et al,[23] 2010	−0.03 (0.20)	0.97 (0.64-1.40)
Random-effects model		0.86 (0.77-0.95)
Heterogeneity: I^2 = 0%, τ^2 = 0, P = .52		
Suicide attempt 4 y following treatment		
Droitcourt et al,[9] 2019	−0.21 (0.07)	0.81 (0.71-0.92)
Sundström et al,[23] 2010	0.00 (0.17)	1.00 (0.72-1.42)
Random-effects model		0.85 (0.72-1.00)
Heterogeneity: I^2 = 23%, τ^2 = 0.0050, P = .26		
Suicide attempt 5 y following treatment		
Droitcourt et al,[9] 2019	−0.25 (0.08)	0.78 (0.66-0.92)
Sundström et al,[23] 2010	0.00 (0.15)	1.00 (0.73-1.34)
Random-effects model		0.85 (0.68-1.08)
Heterogeneity: I^2 = 49%, τ^2 = 0.0153, P = .16		
Suicide attempt 10 y following treatment		
Chen et al,10 2019	−0.02 (0.36)	0.98 (0.40-1.62)
Sundström et al,[23] 2022	0.04 (0.11)	1.04 (0.83-1.26)
Random-effects model		1.04 (0.85-1.26)
Heterogeneity: I^2 = 0%, τ^2 = 0, P = .88		
Test for subgroup differences: χ^2_7 = 4.74, P = .69		



Epidemiological Assessor's comments:

The authors explicitly state that they followed an a priori protocol registered with PROSPERO, and PRISMA and MOOSE reporting guidelines are included in the supplementary materials, enhancing transparency and demonstrating thoroughness in reporting. The use of four major databases (PubMed, Embase, Web of Science, and

Scopus) and hand-searching bibliographies, combined with the wide-ranging search terms, reflects a comprehensive search strategy. Dual independent screening by two authors was conducted, and a standardised data extraction sheet used to ensure consistency in capturing study-level data, although it is not clear how disagreements between reviewers were resolved.

The authors used the Newcastle-Ottawa Scale for study-level bias assessment (a widely recognised and appropriate tool) and clearly describe their thresholds (high, moderate, low) for grading study quality. The use of GRADE to evaluate the quality of outcome-level evidence further adds robustness to the approach. Random-effects models were used to account for between study heterogeneity.

Overall, the meta-analysis was largely conducted in line with best practice methodology. Minor limitations of the meta-analysis include limiting included studies to those published in English, although geographic diversity was identified, with included studies having been conducted across Asia, Australasia, Europe, and North America.

However, the authors note several limitations of the underlying studies included in the meta-analysis. Most studies (19 out of 25) were categorised as having a moderate (16) or high risk (3) of bias. This suggests potential concerns regarding the overall quality of evidence. The most frequent issue was a lack of demonstration that the outcome of interest was not present at the start of the study. The authors note that it is plausible that patients deemed to be at higher risk of psychiatric illness were less likely to receive isotretinoin, which may have resulted in an underestimation of the psychiatric risks of isotretinoin in these observational studies. It is notable that no randomised controlled trials were included in the meta-analysis.

Although 25 studies were included, each outcome was only assessed in 2 or 3 studies, meaning there was insufficient numbers of studies to perform subgroup analyses (e.g. by study design, geographic location, sex) or to assess publication bias. The majority of studies only adjusted for age and sex, without accounting for other potential confounders, such as severity of acne, medical comorbidities, or socioeconomic status, Furthermore, estimates for the relative risk of depression and suicide attempts had wide confidence intervals due to imprecision, meaning it is unable to exclude the potential for meaningful increased risks for these outcomes.

Whilst the pooled epidemiological evidence from this meta-analysis suggests there is no increased risk of suicide or psychiatric conditions among isotretinoin users at a population level, the results are limited by heterogeneity and imprecision. The authors conclude that clinicians should continue to monitor patients for signs of mental distress during isotretinoin treatment.

Of the 24 studies included in the meta-analysis, 5 were published from 2021 onwards. These included Chen (2022), Kridin (2023), Paljarvi (2022), Ugonabo (2021), and Vona-Giralt (2023), all of which are discussed in this assessment.

Additional papers identified by the MHRA

AlGhofaili FA. Isotretinoin Use and Risk of Depression in Acne Vulgaris Patients in Riyadh, Saudi Arabia. Cureus. 2021 Mar 3;13(3):e13680. doi: 10.7759/cureus.13680.

Aim

To estimate the prevalence of depression among patients with acne vulgaris before and after treatment with isotretinoin in Riyadh, Saudi Arabia.

Methods

This was a prospective study of 179 randomly selected new patients attending a tertiary center, King Khalid University Hospital (KKUH) who received treatment for acne vulgaris. Patients were divided into two groups based on the treatment received: the isotretinoin group and the second group using other treatments, including Retin-A (tretinoin) and Tazorac (tazarotene) both topical retinoids. Patients who suffered from acne vulgaris and had been receiving isotretinoin or other treatment modalities for up to six months were included.

Patients were asked to self-report if they developed any depression symptoms or not and the severity of these symptoms was assessed. Patients were divided into two groups based on the treatment modality that they received. Depression severity was measured in participants after three and six months of isotretinoin use using the Beck Depression Inventory (BDI), with higher scores indicating more severe depression. Patients were excluded if they did not fulfill the previous criteria or did not administer isotretinoin for the specified period. For patients in the isotretinoin group, oral isotretinoin was administered at a standard cumulative dose of 150 mg/kg as a daily dose of about 0.5 mg/kg.

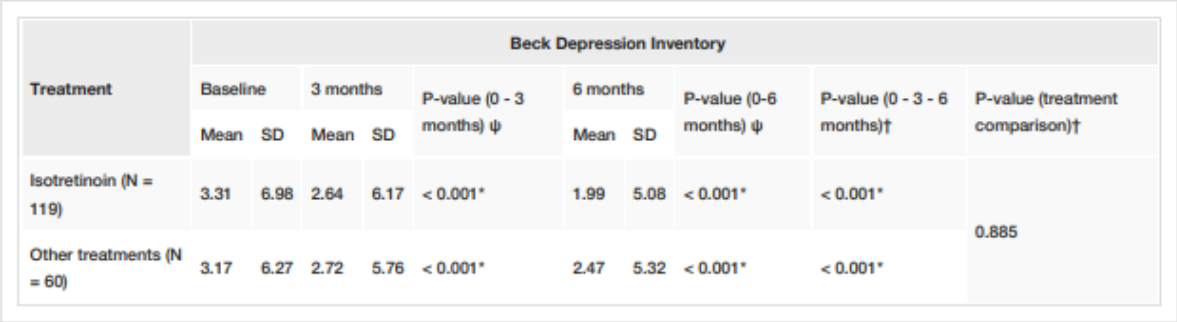
Results

A total of 179 patients participated in the current study of which 119 were treated with isotretinoin and 60 were managed using other treatments (Retin-A and Tazorac). The mean age for all participants was 21.35 ±2.96 years.

The mean BDI score at the baseline was 3.31 ± 6.98 for isotretinoin and 3.17 ± 6.27 for other treatments. Compared to the baseline, patients using the isotretinoin showed a significant reduction in depression scores at three months (2.64 ± 6.17; P<0.001), six months (1.99 ± 5.08; P<0.001), and across all follow-up points (P<0.001).

Similarly, there was a significant reduction in depression scores in patients that were managed with other treatments, including three months follow-up (2.72 ± 5.76; P<0.001), six months follow-up (2.47 ± 5.32; p-value < 0.001), and across all follow-up points (P<0.001).

However, there was no statistically significant difference when comparing the changes of the BDI score in isotretinoin and other treatment groups (P0.885) (Table *2*).



Treatment	Beck Depression Inventory								
	Baseline		3 months		P-value (0 - 3 months) ψ	6 months		P-value (0-6 months) ψ	P-value (0 - 3 - 6 months)†	P-value (treatment comparison)†
	Mean	SD	Mean	SD		Mean	SD			
Isotretinoin (N = 119)	3.31	6.98	2.64	6.17	< 0.001*	1.99	5.08	< 0.001*	< 0.001*	0.885
Other treatments (N = 60)	3.17	6.27	2.72	5.76	< 0.001*	2.47	5.32	< 0.001*	< 0.001*	

TABLE 2: Changes in Depression Scores from Baseline and up to Six Months

ψ Paired t-test

† Repeated measures analysis of variance (ANOVA)

* Statistically significant

N: numbers; SD: standard deviation

Regarding depression categories, the majority of the patients were normal at baseline, whether in the isotretinoin group (91.60%) or the other treatment group (91.67%). Compared to the baseline, patients using isotretinoin showed a significant change in the distribution of depression categories at three months (P = 0.011), six months (P = 0.010), and across all follow-up points (P< 0.001). Nevertheless, no similar significant changes were detected among the patients managed with other treatments, when comparing the baseline to three months follow-up (p-value = 0.157), six months follow-up (P = 0.157), and across all follow-up points (P= 0.333).

Authors' conclusions

The study showed no correlation between developing depression and isotretinoin administration during acne treatment. On the other hand, acne management, whether by isotretinoin or by other modalities, is significantly associated with reduced depression symptoms. The results of this study are in conflict with many previous studies done on isotretinoin and depression. Therefore, more studies studying the correlation in acne patients are needed among tertiary centres in Saudi Arabia.

Epidemiological Assessor's comments

The study has several limitations including the small sample size with only 179 patients in the cohort. The study was conducted in a tertiary centre in Saudi Arabia and it is unclear how representative the patients are of the wider population and if they can be generalised to other countries.

The comparator group consisted of patients exposed to topical retinoid treatments. It is unclear if the isotretinoin group had previously attempted topical treatment and how effective it was in treating their acne. There is the potential for confounding by indication due to acne severity. Furthermore, due to the study design, the analyses were not adjusted for any potential confounders and the only baseline characteristics measured were age, sex, martial status and educational attainment level.

Whilst depression was assessed using a validated questionnaire, it is unclear if patients were aware of the study hypothesis which could have influenced their responses leading to response bias.

Overall, whilst this study suggests isotretinoin is not associated with an increased risk of depression, the limitations identified limit the ability to advance the understanding of the association between isotretinoin psychiatric risks.

Chen YH, Wang WM, Chung CH, Tsao CH, Chien WC, Hung CT. Risk of psychiatric disorders in patients taking isotretinoin: A nationwide, population-based, cohort study in Taiwan. J Affect Disord. 2022 Jan 1;296:277-282. doi: 10.1016/j.jad.2021.09.055.

Aim

To assess the risk of psychiatric conditions in patients with acne who are taking isotretinoin in a Taiwanese population.

Methods

The study used anonymised data from the National Health Insurance Research Database (NHIRD), which includes contracts with 97% of medical providers and was established in 1995 providing healthcare for over 98% of Taiwanese people.

This cohort study selected 53,184 patients who were newly diagnosed with acne (ICD-9-CM code 706.1) between 2000 and 2015 from the NHIRD. Patients were excluded if they had been diagnosed with suicidality, attention deficit hyperactivity disorder (ADHD), schizophrenia, bipolar disorder (BD), major depressive disorder (MDD), manic disorder, personality disorder, obsessive-compulsive disorder (OCD), phobic disorder, or anxiety before 2000, or before their first clinical visit for acne. Patient were also excluded if they were aged <20 years old or had taken isotretinoin for <1 month. For every acne patient treated with oral isotretinoin included, two controls diagnosed with acne without oral isotretinoin treatment were included as the control group and were matched (1:2) for age, sex, and index year.

Patient follow-up time started from the index date and continued until the onset of psychiatric conditions or the end of 2015 or withdrawal from the NHI program. Outcomes included suicidality (ICD-9-CM code E950–E959), ADHD (ICD-9-CM code 314.0–314.01), schizophrenia (ICD-9-CM code 295–295.95), BD (ICD-9-CM code 296.4–296.7), MDD (ICD-9-CM code 296.2–296.36), manic disorder (ICD-9-CM code 296.0–296.16), personality disorder (ICD-9-CM code 301–301.9), OCD (ICD-9-CM code 300.3), phobic disorder (ICD-9-CM code 300.20–300.29), anxiety (ICD- 9-CM code 300.0–300.09).

The covariates were sex, age group (20–29, 30-39, 40-49, 50-59, ≥60 years), comorbidity, level of medical care, season, residential area (north, south, center, and east of Taiwan), and urbanization level of their residential area. Comorbidities were classified according to ICD-9- CM codes and evaluated by the Charlson Comorbidity Index (CCI). A higher CCI value indicated a higher comorbidity burden.

Results

The cohort consisted of 9981 participants who received isotretinoin and 19,962 participants in the control cohort. The mean age of subjects was 38.00 ± 20.27 years and 65.42% were women. Mean follow-up time was 10.03 ± 9.98 years in patients with isotretinoin treatment and 9.97 ± 9.94 years in controls. At the end of the follow-up period, 11,401 participants (38.08%) developed psychiatric disorders, which included 3822 patients who underwent isotretinoin treatment (38.29%) and 7579 controls (37.97%).

Patients treated with isotretinoin did not have a higher risk of psychiatric disorders compared with the control cohort. After adjusting for age, gender, and comorbidity (CCI index), the adjusted HR (aHR) of psychiatric disorders was 1.009 (95% CI: 0.422–1.696, *P* = 0.517; Table 2). The isotretinoin-treated cohort did not have an increased risk of developing anxiety (aHR: 1.022; 95% CI: 0.428–1.711; *P* = 0.542), OCD (aHR: 1.201; 95% CI: 0.503–2.007; *P* = 0.415), manic disorder (aHR: 1.014; 95% CI: 0.422–1.709; *P* = 0.513), MDD (aHR: 0.953; 95% CI: 0.398–1.613; P = 0.528), BD (aHR: 1.053; 95% CI: 0.433–1.787; *P* = 0.504), schizophrenia (aHR: 1.000; 95% CI: 0.418–1.692; *P* = 0.573), or suicidality (aHR: 0.982; 95% CI: 0.398–1.622; *P* = 0.588). The subgroup analysis of gender showed no increased risk in either male or female patients (aHR: 1.002, 95% CI: 0.418–1.680, *P* = 0.524; aHR: 1.013, 95% CI: 0.434–1.702, *P* = 0.468, respectively). Furthermore, there was no elevated risk of psychiatric disorders across any of the age groups of patients who received isotretinoin treatment.

Table 2
Factors of psychiatric disorders, gender, and age subgroups by using Cox regression.

Isotretinoin	With			Without (Reference)			With vs. Without (Reference)			
Subgroups	Events	PYs	Rate (per 10^5 PYs)	Events	PYs	Rate (per 10^5 PYs)	Adjusted HR	95% CI	95% CI	*P*
Overall psychiatric disorders	3822	99,616.12	3836.73	7579	209,233.12	3622.28	1.009	0.422	1.696	0.517
Anxiety	1045	99,616.12	1049.03	2,045	209,233.12	977.38	1.022	0.428	1.711	0.542
OCD	3	99,616.12	3.01	5	209,233.12	2.39	1.201	0.503	2.007	0.415
Manic disorder	2345	99,616.12	2354.04	4627	209,233.12	2,211.41	1.014	0.422	1.709	0.513
MDD	131	99,616.12	131.50	275	209,233.12	131.43	0.953	0.398	1.613	0.528
Bipolar disorder	10	99,616.12	10.04	19	209,233.12	9.08	1.053	0.433	1.787	0.504
Schizophrenia	3	99,616.12	3.01	6	209,233.12	2.87	1.000	0.418	1.692	0.576
Suicide	301	99,616.12	302.16	614	209,233.12	293.45	0.982	0.398	1.622	0.588
Gender										
Male	1745	34,476.10	5061.48	3325	68,926.12	4824.01	1.002	0.418	1.680	0.524
Female	2077	65,140.02	3188.52	4254	140,307.00	3031.92	1.013	0.434	1.702	0.468
Age group (yrs)										
20–29	1311	34,522.82	3797.49	2633	73,035.31	3605.11	1.003	0.420	1.687	0.489
30–39	882	23,244.81	3794.40	1772	49,378.82	3588.58	1.007	0.422	1.699	0.484
40–49	786	20,819.48	3775.31	1532	43,812.97	3496.68	1.029	0.430	1.728	0.473
50–59	699	17,785.39	3930.19	1308	36,392.04	3594.19	1.042	0.436	1.753	0.465
≧60	144	3234.62	4451.84	334	6613.98	5049.91	0.840	0.353	1.418	0.570

PYs = Person-years; Adjusted HR = Adjusted Hazard ratio: Adjusted for the variables listed in Table 1.; CI = confidence interval.

Subgroup analyses were conducted by grouping isotretinoin-treated patients according to dosage: 3324 patients received ≤ 20 mg per day, and 6657 patients received > 20 mg per day. Compared with controls, there was no increase in risk of psychiatric disorders in patients who received different doses of isotretinoin (≤ 20 mg per day, aHR: 0.892, 95% CI: 0.371–1.501, *P* = 0.539; >20 mg per day, aHR: 1.068, 95% CI: 0.446–1.798, *P* = 0.422). According to treatment duration, there were 5896 patients with a treatment duration ≤6 months, and 4085 with treatment duration > 6 months for the subgroup analysis of isotretinoin-treated patients. Compared with controls, there was no increase in risk of psychiatric disorders in patients who received different durations of isotretinoin treatment (≤6 months, aHR: 0.924, 95% CI: 0.392–1.612, *P* = 0.526; >6 months, aHR: 1.196, 95% CI: 0.488–2.004, *P* = 0.473).

Authors' conclusions

The study findings do not support an association between isotretinoin treatment and the development of psychiatric disorders. It was also shown that patients with acne who undergo isotretinoin treatment at either a higher dose or longer duration show no increased risk of developing psychiatric disorders. However, close monitoring would be prudent in patients more prone to depression or other psychiatric conditions throughout the isotretinoin treatment course. Further prospective studies focusing on patients with specific psychiatric conditions would be of significant value.

Epidemiological Assessor's comments:

Whilst this was a relatively large study, there are several limitations. The patients included were from a Taiwanese population. The prevalence of psychiatric disorders will vary across different populations and regions and so this study may have limited generalisability. The study was also based on insurance data, so it is unclear if the data

would have captured mild psychiatric conditions for which patients did not seek healthcare treatment and were therefore not recorded.

The comparator cohort comprised patients with an acne diagnosis but who were unexposed to isotretinoin. It is therefore unclear what, if any, alternative acne treatments the comparator group were exposed to and so there could be differences in the underlying acne severity between the isotretinoin cohort and the comparator cohort resulting in potential confounding by indication.

There is the potential for residual confounding by some variables which could not be measured including socioeconomic statis, BMI, smoking and lifestyle factors as acknowledged by the authors.

Overall, whilst this study suggests isotretinoin is not associated with the risk of psychiatric outcomes, there are several limitations, particularly around the comparator, which limit the ability to advance the understanding of the association between isotretinoin psychiatric risks.

Droitcourt C, Kerbrat S, Raby M, Laurent C, Travers D, Balusson F, Oger E, Dupuy A. The risk of hospital admission for an acute-onset psychiatric disorder in adolescents and adults treated with isotretinoin: a French, nationwide, population-based, case-time-control study. Dermatology. 2024 Dec 21:1-20. doi: 10.1159/000542626.

Aim

To determine whether adolescents and young adults have an elevated risk of acute-onset psychiatric disorder requiring hospital treatment within 2 months of starting isotretinoin treatment.

Methods

The study used the French national health insurance database (Système National des Données de Santé, SNDS), 2010-2015. The study design was a case-time-control study nested in a nationwide cohort of all French adolescents and young adults aged 10 to 25 years treated with isotretinoin. The outcome was an acute-onset psychiatric disorder requiring hospitalization (including anxiety, depressive, mood, adjustment and psychotic disorders).

The case-time-control study assesses the probability of isotretinoin initiation within a two-month period before an acute-onset psychiatric disorder requiring hospitalization compared to the probability within a similar time-period before the aforementioned period. This design consists of two self-adjusted analyses, a first case-crossover analysis (among “cases”, i.e. individuals who experienced an acute psychiatric event) and a second case-crossover analysis (among individuals who did not experience an acute-onset psychiatric disorders requiring hospitalization by the time the above mentioned cases did: hence, those individuals, named isotretinoin exposure-trend control, are matched on calendar time to “individual cases”). Individuals are their controls as two adjacent periods of their time are compared.

A first crossover (CO) analysis was performed in patients hospitalized for an acute-onset psychiatric disorder (cases) and starting a course of oral isotretinoin at one moment in time. The date of hospital admission for an acute-onset psychiatric disorder was taken as the index date. Two periods were defined with regard to the index date: a risk period in the 2 months before the index date and a reference period from 2 months to 4 months before the index date. The data was then searched for the initiation of isotretinoin treatment in the risk period or the reference period. Each case was classified as starting isotretinoin (yes/no) during the risk period and during the reference period. In

the crossover analysis, each case (a patient hospitalized for an acute-onset psychiatric disorder) served as his/her own control which allows self-adjusting for time invariant characteristics not recorder in medico-administrative healthcare databases such as social factors or psychiatric family history. Each case was randomly matched for their birth date and sex with five different isotretinoin exposure-trend controls (i.e. patients lacking a hospital diagnosis of acute-onset psychiatric disorder) from the isotretinoin population and selected at a time corresponding to that inclusion of the cases considered for the first case crossover analysis (index date). The controls' initiations of isotretinoin treatment during the risk period or during the reference period were also searched.

Conditional logistic regression models were used to estimate the odds ratios (OR) of acute-onset psychiatric disorders associated with isotretinoin over the risk period compared with the reference period. To take into account the variation of time-exposure isotretinoin, conditional logistic regression model was used to estimate the odds ratios of acute-onset psychiatric disorders associated with isotretinoin over the risk period compared with the reference period. Finally, the ratio of odds ratios (odds ratio for CO cases divided by odds ratio for CO variation of time-exposure isotretinoin controls) yielded an estimate for the association of isotretinoin initiation and the risk of acute-onset psychiatric disorders controlling for isotretinoin exposure-trend bias.

Results

2,284 acute-onset psychiatric disorders requiring hospitalization were recorded for the study population of 262,786 patients. Among the patients with at least one psychiatric event, 88 had started taking isotretinoin in the risk period (0 to 2 months before the date of the event), versus 81 in the reference period (2 to 4 months before the event). A comparison with the 383 and 355 time-trend matched controls who started taking isotretinoin in the risk and reference periods, respectively, yielded a case-time-control OR (95%CI) of 1.01 (0.72-1.41).

Authors' conclusions

The risk of developing acute-onset psychiatric disorders requiring hospitalization was not elevated in the 2 to 4 months following the initiation of isotretinoin.

Epidemiological Assessor's comments

The SNDS database cover 98% of the population of the France and therefore should be largely representative of the population. Due to the study design and data source, loss to follow-up may not have been an issue as highlighted by the authors.

The composite outcome was based on hospitalisation for a severe acute-onset psychiatric event so the study will have excluded psychiatric diagnoses that did not lead to a hospitalisation. The study findings cannot be generalised to acute-onset psychiatric diagnoses managed in primary care, which could be milder in severity. Due to the use of a composite outcome, it was not possible to evaluate the risk according to specific psychiatric disorder subtypes.

Whilst the to the choice of study design is appropriate for outcomes with an abrupt onset it was not possible to assess the risk compared with a comparator group treated with alternative acne treatments (e.g. antibiotics).

Whist this study suggests the risk of developing acute-onset psychiatric disorders requiring hospitalisation was not elevated in the 2 to 4 months following the initiation of isotretinoin, the use of a composite outcome and outcome case definition means it is not possible to evaluate the risk of specific psychiatric disorder subtypes which did not require hospitalisation but were managed in primary care.

Hekmatjah J, Chat VS, Sierro TJ, Read C, Kassardjian AA, Armstrong AW. Differences in Depression and Distress Between Acne Patients on Isotretinoin vs Oral Antibiotics. J Drugs Dermatol. 2021 Feb 1;20(2):172-177. doi: 10.36849/JDD.5559.

Aim

To determine whether differences exist in mental health outcomes between acne patients treated with isotretinoin versus oral antibiotics (doxycycline, minocycline or tetracycline).

Methods

The study used cross-sectional data from the 2004-201 Household Component of the Medical Expenditure Panel Survey (MEPS). The survey represents a national non-institutionalised sample of the United States population. Each household is surveyed five times over a two-year period. Each survey includes estimates of healthcare use, expenditures, sources of payment and health insurance coverage. Surveys also include information on respondents' health status, demographic/socioeconomic characteristics, employment status, access to health care and mental health status. The 2004-2017 response rate ranged from 46% to 63%.

The study population consisted of patients who reported a diagnosis of acne, were on isotretinoin or oral antibiotics and completed both of the following mental health outcomes measures; Patient Health Questionnaire-2 (PHQ-2) and Kessler 6-item Psychological Distress Scale (K6). Patients self-reporting a diagnosis of acne were identified based on ICD codes. The number of patients who were prescribed isotretinoin or oral antibiotics (doxycycline, minocycline or tetracycline) were identified. Acne patients completed both the PHQ-2 and K6 during treatment with isotretinoin or oral antibiotics. Lower scores on both measures indicate better mental health outcomes.

The exposure was defined as acne treatment with either isotretinoin or oral antibiotics. The outcomes were depression symptoms and psychological distress.

Results

9,046,894 (weighted) patients were identified who were prescribed either isotretinoin (13%) or an oral antibiotic (87%) and completed both the PHQ-2 and K6 questionnaires. The mean age was 25.34 years for isotretinoin exposed patients and 34.37 years for oral antibiotic patients.

After adjusting for socio-demographic characteristics, patients on isotretinoin had fewer depressive symptoms that patients on oral antibiotics as measured by mean PHQ-2 scores; isotretinoin= 0.280 vs oral antibiotics=0.656, difference-0.337, $p<0.01$. The adjusted comparison also showed patients on isotretinoin had less psychological distress than patients on oral antibiotics as measured by K6 scores; isotretinoin=2.494 vs oral antibiotics=3.433, difference=0.759, $p=0.043$.

Authors' conclusions

The study showed isotretinoin was associated fewer depressive symptoms and less psychological distress in acne patients as compared to those on oral antibiotics. The negative psychological state of acne patients is likely attributable to having acne itself rather than potential iatrogenic effects of systemic treatments. Therefore, in treating patients with moderate-to-severe acne, dermatologists need to account for patients' physical and mental health burdens as well as accurately assess the safety profiles of systemic treatments.

Epidemiological Assessor's comments

The study has several limitations. This was a cross-sectional study which asked patients to self-report drug exposure and mental ill health through questionnaires at a given point in time. It was therefore not possible to determine the temporal association between acne drug exposure and when symptoms of mental ill health started. Patients were not asked to report information regarding their severity of acne and any treatments they received prior to starting isotretinoin treatment and whether it effective or not in treating their acne. Given these limitations, this study is unlikely to advance understanding of the association between isotretinoin and psychiatric adverse effects.

Öğüt Ç, Öğüt ND. No association between isotretinoin and impulsivity in patients with moderate-to-severe acne vulgaris. Int J Dermatol. 2024 Apr;63(4):484-490. doi: 10.1111/ijd.16997. Epub 2023 Dec 22. PMID: 38140757

Aim

This study aimed to examine impulsive characteristics using self-report scales and behavioural tasks concurrently in patients with acne vulgaris (AV) before and after isotretinoin treatment and to assess the link between impulsivity and suicidality.

Methods

Participants were recruited between February 2023 and August 2023 from Usak Training and Research Hospital Dermatology and Venereology Outpatient Clinic. Participants between the ages of 18 and 45 presenting for isotretinoin treatment of moderate-to-severe AV were eligible. Acne severity was assessed by the dermatologist at baseline according to Pillsbury et al. The inclusion criteria were as follows: age 18–45 years, high school or higher education level, moderate-to-severe AV diagnosis, and initiation of isotretinoin treatment plan in place.

The exclusion criteria were prior use of isotretinoin and neurological/medical disorders affecting cognitive functioning. Patients who scored high on depression, anxiety, and suicide related self-report scales at the first interview were referred to the psychiatry outpatient clinic for treatment. Patients who started psychiatric treatment were excluded from the study. In addition, patients who did not apply for dermatology control in the third month of the follow-up were excluded from the study.

This study was prospective observational study comparing impulsivity, depression, and anxiety severity at baseline and after 3 months in AV patients prescribed isotretinoin. Secondary outcome measures were to assess suicidality to investigate its association with isotretinoin treatment. Patients were offered the option to participate in the study only after they had made a therapeutic choice regarding their acne therapy. Isotretinoin was prescribed at 0.5 mg/kg per day (20–40 mg/day). Participants received a dermatological and psychiatric assessment at baseline (before starting isotretinoin medication) and again in the third month of treatment.

Study forms, self-report scales, and behavioural tasks were administered in identical order in a quiet 3 m x 3 m room. Participants performed the behavioral tasks (GNG and BART) using the same computer.

The following instruments and tasks performed are outlined below:

Instrument/task	Purpose

Columbia-Suicide Severity Rating Scale (CSSRS)	Semi-structured interview-designed instrument assessing suicidal ideation, suicidal behaviour and non-fatal self-injury in clinical trials.
Beck Anxiety Inventory (BAI)	Self-report instrument measuring anxiety symptom severity. Higher scores indicate more severe symptoms.
Beck Depression Inventory (BDI)	Self-report instrument measuring depression symptom severity. Higher scores indicate more severe symptoms.
Barratt Impulsivity Scale (BIS)	Self-report instrument that measures the impulsiveness. Higher scores indicate more severe impulsive features.
Go/No-go Task (GNG	Computerised behavioural task that measures response inhibition (motor impulsivity) and attention.
Balloon Analogue Risk Task (BART)	Computerised behavioural task that measure cognitive impulsivity-related risk-taking behaviour.

Results

In total, 17 of the 30 participants completed the study with the remaining 13 lost to follow-up.

The most common locations of the acne lesions were the cheeks, chin, forehead, back, chest, and nose, respectively. The duration of acne lesions ranged in length from 1 to 10 years (mean: 4.7 ±2.4 years). The mean cumulative dose of isotretinoin treatment was 2,860 mg/3 months.

According to self-report scale scores, 35% of the patients in this study had mild depression, 18% had moderate depression, and 53% had mild anxiety, 12% had moderate anxiety, and 12% had severe anxiety at the beginning of the study. There was a significant reduction in BAI and BDI scores at follow-up. At the end of the follow-up, 12% of the patients had mild depression, and 53% had mild anxiety. There were no patients with moderate or severe anxiety or depression symptoms.

Participants' performance in the attentional domain measured during the GNG test improved at follow-up. There was no difference in self-report scales and behavioural task scores related to impulsivity between before and after follow-up.

There was a positive correlation between the change in total impulsivity scores obtained with the BDI and the change in depression ($r = 0.686$; $P = 0.02$) and anxiety ($r = 0.514$; $P = 0.035$) scores during the follow-up period.

No self-harm behaviour, suicidal ideation, or suicidal behaviour was detected in the participants during the study period. While four patients (24%) stated that they had thoughts related to death at the beginning of the study, they reported these thoughts did not remain at the end of the follow-up. The change in depression ($t = -2.766$; $P = 0.014$) and self-report impulsivity ($t = -2.532$; $P = 0.023$) scores was found to be significantly higher in those whose death thoughts improved compared to the other participants.

Authors' conclusions

To the best of the authors' knowledge, no previous study has evaluated the effect of isotretinoin on impulsivity. The study showed no significant change in patients' response inhibition in the GNG test after isotretinoin use. The findings also suggest that the use of isotretinoin does not impair the response inhibition process. The study also showed no increase in impulsive decision-making tendencies after isotretinoin treatment. No significant change was observed in the impulsivity dimensions of the patients assessed by self-report scales and behavioural tasks because of isotretinoin treatment. The decreases in depression and anxiety symptoms were correlated with the decreases in the severity of self-reported impulsivity. It was observed in some participants whose self-report and behavioural impulsivity scores increased during the follow-up; however, the sample size was insufficient to compare these subgroups.

18% of the participants had moderate-to-severe depression, and 24% had moderate-to-severe anxiety symptoms. The high prevalence of anxiety and depression in this study has been repeatedly shown in the literature. However, significant improvement in depression and anxiety symptoms was observed in patients using isotretinoin during the follow-up period. No patients had moderate or severe depression or anxiety symptoms at the end of follow-up.

In this study, it was shown that patients' attention performance improved after isotretinoin treatment. This finding is consistent with studies showing increased attention performance with isotretinoin treatment. Attention is one of the main symptoms of depression and anxiety disorders. Therefore, improvement in attention performance may be related to mood symptoms.

This study showed that death thoughts detected in four patients at the beginning of the study improved at the end of isotretinoin treatment. No patient with death thoughts and suicidal ideation was observed at the end of the follow-up. This finding indicates that isotretinoin is a safe treatment option in patients with AV. Nevertheless, it has been reported that some subgroups may be particularly vulnerable to suicidal thoughts triggered by isotretinoin. Suicide risk may increase in certain subgroups with increased impulsivity with isotretinoin treatment. However, this study's sample size was insufficient to detect these risky subgroups. Large-sample studies may help identify possible risky subgroups for isotretinoin treatment.

Epidemiological Assessor's comments:

The main limitation of this study is the small sample and high drop-out rate which limited some analyses. The study was also conducted in a single centre which may limit the generalisability of the study findings. There was also no comparator group which prevented the ability to contextualise the results.

Overall, a study with a higher number of participants and a comparator group would be of benefit to further explore the correlation between impulsivity and attention and depression and anxiety in acne patients so that more robust conclusions can be made.

Orenay OM, Temel B, Capci AK, Bal ZI, Karaosmanoglu N. Evaluation of isotretinoin effects on depression, sleep apnea and sleep quality. Cutan Ocul Toxicol. 2024 Jun;43(2):129-133. doi: 10.1080/15569527.2024.2340435.

Aim

To evaluate the effects of isotretinoin on depression, sleep apnoea and sleep quality.

Methods

A total of 42 acne vulgaris patients who were admitted to the Department of Dermatology of Ankara Training and Research Hospital and started isotretinoin were included in the study.

Patients who had any systemic disease, depression or other psychiatric disorders, sleeping disorders, and sleep apnea were not included in the study. The ones who had a BMI ≥30 were also not included. A daily dose of 0.5–1 mg/kg isotretinoin was initiated. The total cumulative dose of isotretinoin was also calculated and recorded. The severity of acne in the patients was assessed using the global acne scoring system and classified as mild (1–18 points), moderate (19–30 points), or severe (≥31 points).

All of the patients were asked to fill out the questionnaires at baseline and 12th weeks of treatment including the Beck Depression Inventory (BDI), the Berlin Questionnaire (BQ), and the Pittsburgh Sleep Quality Index (PSQI). The scores of BDI, BQ, and PSQI were calculated and compared at baseline and 12th weeks of isotretinoin.

Results

A total of 42 patients were included in this study. Of the 42 patients, 14 (33.3%) were male and 28 (66.7%) were female. The mean age was 20.47 ± 4.01 years. The mean BMI of the patients was 22.08. All patients were living at home with their families except for one patient who was living in the dormitory. Two (4.8%) of the patients had mild acne, 21 (50%) had moderate acne and 19 (45.2%) had severe acne. The mean total cumulative dose of isotretinoin was 2911 milligrams (mg) at the end of the 12th week of treatment. The mean time of sleep of the patients was 8 h 4 min per day.

The scores of BDI, BQ and PSQI questionnaires of all patients were evaluated at the first and third month of treatment. 18 (42.9%) of the patients had no-minimal depression, 13 (31%) had mild, 3 (7.1%) had moderate, and 8 (19%) had severe depression. At the end of 3rd month of treatment; 20 (47.6%) of the patients had no-minimal depression, 11 (26.2%) had mild depression, 8 (19%) had moderate depression and 3 (7.1%) had severe depression. It was found that the overall BDI scores decreased compared to the baseline, but there was no statistically significant difference ($p = 0.53$).

There was no statistically significant difference between the first and 3rd months of treatment in terms of total and three subgroup scores of BQ ($p = .5$, $p = 0.52$, $p = 0.62$, $p = 1$).

There was no statistically significant difference between the first and third months of treatment in terms of PSQI scores ($p = 0.035$) and also between PSQI subgroups ($p = 0.55$, $p = 0.42$, $p = 0.89$, $p = 0.4$, $p = 0.4$, $p = 1$, $p = 0.3$). At baseline, 23 patients had a total PSQI score of ≥5. After 12 weeks of treatment, this number increased to 29. However, there was no statistically significant difference between the first and 3rd months of treatment ($p = 0.17$)

There was a positive correlation between the BDI scores and the PSQI scores within 3 months.

Authors' conclusions

This study showed no association between isotretinoin and depression, sleep apnoea, or sleep quality. The literature contains only a few case reports of sleep disturbances due to isotretinoin treatment and only one study in a small group of patients. Further studies with larger sample groups and more objective examinations are needed to reveal the exact effects of isotretinoin on sleep quality and depression.

Epidemiological Assessor's comments

This study has several limitations including the small number of patients and lack of comparator group with which to contextualise the results. Both depressive and sleep

apnoea symptoms were evaluated through questionnaires and no physical exams were conducted.

Given the limitations of this study, it is unlikely to advance understanding of the association between isotretinoin and the risk of depression and sleep apnoea.

Ugonabo N, Love E, Wong PW, Rieder EA, Orlow SJ, Kim RH, Nagler AR. Psychiatric disorders and suicidal behaviour in patients with acne prescribed oral antibiotics versus isotretinoin: Analysis of a large commercial insurance claims database. J Am Acad Dermatol. 2021 Oct;85(4):878-884. doi: 10.1016/j.jaad.2021.01.107.

Aim

To use a large population database to evaluate the prevalence of major depressive disorder, other psychiatric conditions and suicidal behaviour in persons with acne who received oral antibiotics or isotretinoin as compared to their peers.

Methods

The data source was the IBM MarketScan Commercial Database, which is an insurance claims database that includes between 20-40 million beneficiaries from 150 large employers in the United States. The database includes claims made between 01/01/2011-31/12/2017.

This retrospective cohort study identified patients with moderate to severe acne who were prescribed isotretinoin or antibiotics and who were aged 12-35 years. Patients were included if they had at least two ICD diagnosis codes for acne vulgaris, acne conglobate and/or acne unspecified within an 18-month period and were seen by a dermatologist within this 18-month period and were prescribed oral antibiotics and/or isotretinoin. Patients treated only with topical therapy were excluded.

The study period was defined as 12 months prior to the first antibiotic/isotretinoin fill date, the duration of treatment (ie, the first isotretinoin/antibiotic fill date to the last isotretinoin/antibiotic fill date plus 30 days), and 12 months after treatment with isotretinoin/antibiotic. As part of the inclusion criteria, all patients were required to be continuously enrolled in the database during this time.

The oral antibiotics only study group included patients who met the previously mentioned selection criteria and received at least one 30-day prescription for antibiotic therapy (including cephalosporins, beta lactams, macrolides, and tetracyclines), but not isotretinoin, during the study period described above.

The isotretinoin study group included patients prescribed isotretinoin for any duration during the study period. If patients were prescribed antibiotics and isotretinoin during the study period, they were included in the isotretinoin study group only.

The general population consisted of enrolled patients aged 12 to 35 years who were not diagnosed with acne.

Patients were excluded who had an ICD code for folliculitis, rosacea, ichthyosis, Lyme disease, Rocky Mountain Spotted fever, ehrlichiosis, malaria, and/or pneumonia, as these conditions also may be treated with prolonged antibiotic therapy. Also excluded were patients who had been prescribed medications known to worsen acne, such as systemic steroids, testosterone, progesterone, lithium, phenytoin, epidermal growth factors inhibitors, and isoniazid. Patients who were or became pregnant during the study period were excluded, because this is a contraindication for isotretinoin and certain antibiotics.

Outcomes

The outcomes of interest included the prevalence of all psychiatric disorders, mood disorders, anxiety, mania or psychotic disorder, other mental disorders, psychiatric disorders requiring medication and suicidal behaviour.

Prevalence was defined at the proportion of diagnosis occurrences during the study period divided by the total population.

Results

A total of 72,855 patients aged 12-35 years met inclusion and exclusion criteria for acne patients prescribed antibiotics or isotretinoin. Of these patients, 42,848 were in the antibiotics-only group and 30,012 patients were in the isotretinoin group.

During the study period, 28.7% (2,335,158) of individuals in the general population had a concomitant psychiatric diagnosis. In the group prescribed antibiotics, 24.1% (10,340) had a concomitant psychiatric diagnosis; 10.0% (4297) were diagnosed with a mood disorder, 12.0% (5121) with an anxiety disorder, 1.4% (597) with mania or a psychotic spectrum illness, and 10.5% (4503) with other behavioural disorders. Of the 10,340 patients who were prescribed only antibiotics and who had a concomitant psychiatric diagnosis, 5517 (53%) were diagnosed prior to treatment with antibiotics and 4823 (47%) were diagnosed after initiation of treatment.

In the group prescribed isotretinoin, 23.1% (6926) had a concomitant psychiatric diagnosis, of whom 9.5% were diagnosed with a mood disorder (2837), 10.4% with an anxiety disorder (3132), 1.1% (332) with mania or a psychotic spectrum illness, and 9.8% (2948) with other behavioural disorders. Of the 6926 patients with a psychiatric diagnosis who were prescribed isotretinoin, 3971 (57%) were diagnosed before being treated with isotretinoin and 2955 (43%) were diagnosed following initiation of treatment.

When adjusted for age, sex, and number of days enrolled, patients in the general population had significantly lower odds of having a psychiatric diagnosis when compared to acne patients prescribed isotretinoin (adjusted OR 0.87; confidence interval [95% CI], 0.84, 0.89; P<.0001). Patients in the antibiotics only group had significantly lower odds of having a psychiatric diagnosis when compared to the isotretinoin group (adjusted OR 0.88; 95% CI, 0.85, 0.91; P<.0001).

Suicidal behaviour was less prevalent in both the antibiotics only group (0.67%; 289 patients) and isotretinoin group (0.60%; 180 patients) than in the general population (0.9%; 69,435). When controlling for age, sex, and number of days enrolled, individuals in the general population had significantly higher odds of demonstrating suicidal behaviour than acne patients prescribed isotretinoin (adjusted OR 1.47; 95% CI, 1.27, 1.70; P<.0001, table II).

Table II. Comparison of the prevalence of psychiatric disorders and suicidal behavior in patients prescribed isotretinoin versus antibiotics only versus general population, with isotretinoin as the reference group

	Prevalence	Crude OR* (95% CI)	*P* value	Adjusted OR*,† (95% CI)	*P* value
All psychiatric disorders					
Isotretinoin (n = 30,012)	6926 (23.1%)	-	-	-	-
Antibiotics only (n = 42,843)	10,340 (24.1%)	1.06 (1.02, 1.10)	.001	0.88 (0.85, 0.91)	<.0001
General population (n = 8,123,436)	2,335,158 (28.7%)	1.35 (1.31, 1.38)	<.0001	0.87 (0.84, 0.89)	<.0001
Mood disorder					
Isotretinoin	2837 (9.5%)	-	-	-	-
Antibiotics only	4297 (10.0%)	1.07 (1.02, 1.12)	.010	0.90 (0.85, 0.94)	<.0001
General population	1,032,715 (12.7%)	1.40 (1.34, 1.45)	< .0001	0.97 (0.93, 1.00)	.075
Anxiety disorder					
Isotretinoin	3132 (10.4%)	-	-	-	-
Antibiotics only	5121 (12.0%)	1.17 (1.11, 1.22)	<.0001	0.96 (0.92, 1.01)	.094
General population	1,190,928 (14.7%)	1.47 (1.42, 1.53)	<.0001	0.90 (0.87, 0.94)	<.0001
Mania or psychotic disorder					
Isotretinoin	332 (1.1%)	-	-	-	-
Antibiotics only	597 (1.4%)	1.26 (1.11, 1.45)	.001	1.15 (1.01, 1.32)	.039
General population	188,267 (2.3%)	2.12 (1.91, 2.37)	<.0001	1.76 (1.58, 1.97)	<.0001
Other mental disorders					
Isotretinoin	2948 (9.8%)	-	-	-	-
Antibiotics only	4503 (10.5%)	1.08 (1.03, 1.13)	.003	0.93 (0.88, 0.97)	.002
General population	941,441 (11.6%)	1.20 (1.16, 1.25)	<.0001	0.86 (0.83, 0.89)	<.0001
Psychiatric disorder requiring medication					
Isotretinoin	3860 (12.9%)	-	-	-	-
Antibiotics only	5564 (13.0%)	1.01 (0.97, 1.06)	.62	0.83 (0.80, 0.87)	<.0001
General population	1,437,989 (17.7%)	1.46 (1.41, 1.51)	<.0001	0.89 (0.86, 0.93)	<.0001
Suicidal behavior					
Isotretinoin	180 (0.60%)	-	-	-	-
Antibiotics only	289 (0.67%)	1.13 (0.94, 1.36)	.214	1.00 (0.83, 1.21)	.973
General population	69,435 (0.9%)	1.43 (1.24, 1.66)	<.0001	1.47 (1.27, 1.70)	<.0001

CI, Confidence interval; *OR*, odds ratio.
*Comparison of psychiatric disorders among patients receiving isotretinoin versus antibiotics only versus general population.
†Adjusted for age, sex, and length of time enrolled.

Suicidal behaviour was less prevalent in both the antibiotics only group (0.67%; 289 patients) and isotretinoin group (0.60%; 180 patients) than in the general population (0.9%; 69,435). When controlling for age, sex, and number of days enrolled, individuals in the general population had significantly higher odds of demonstrating suicidal behaviour than acne patients prescribed isotretinoin (adjusted OR 1.47; 95% CI, 1.27, 1.70; P<0.0001) (table II).

Within the isotretinoin group, the prevalence of suicidal behaviour during the year prior to isotretinoin use was 0.22%; during isotretinoin use, including 30 days immediately following last date of prescription fill, the prevalence was 0.10% (P = 0.082); and during the year after isotretinoin, the prevalence was 0.34% (P = 0.004).

Within the antibiotics only group, the prevalence of suicidal behaviour during the year prior to antibiotics only use was 0.24%; during antibiotic use, including 30 days immediately following last date of prescription fill, the prevalence was 0.26% (P = 0.074); and during the year after antibiotic use, the prevalence was 0.20% (P = 0.205).

Between groups, the prevalence of suicidal behaviour during the treatment course, including 30 days after last prescription fill, was 0.10% in the isotretinoin group, which was less than that of the antibiotics only group (0.26%; P = 0.0709, adjusted for duration of treatment) (table III).

Table III. Comparison of the prevalence of suicidal behavior in the treatment period: 1 year before, during,* and 1 year after treatment with antibiotics only versus isotretinoin only

	Suicidal behavior in isotretinoin, n = 30,012		Suicidal behavior in antibiotics only group, n = 42,843		Suicidal behavior in isotretinoin versus antibiotics only
Time period	n (%)	*P* value†	n (%)	*P* value†	*P* value‡
1 year prior to treatment, n (%)	66 (0.22)	-	104 (0.24)	-	.5852
During treatment,* n (%)	29 (0.10)	.082	112 (0.26)	.074	.0709
1 year after treatment, n (%)	101 (0.34)	.004	87 (0.20)	.205	.0006

Some individuals are represented in more than 1 time period.
*"During treatment" is defined as the period between the start of treatment through 30 days after the last prescription is filled.
†Comparison of proportion of suicidal behavior 1 year prior to treatment versus during treatment versus 1 year after treatment, adjusted for duration.
‡Comparison of proportion of suicidal behavior in isotretinoin versus antibiotics only group, adjusted for duration.

Authors' conclusions

Despite the increased prevalence of psychiatric diagnoses in acne patients in the cohort who had been prescribed isotretinoin, suicidal behaviour was less prevalent in this group than in the general population, even when controlling for age, gender, and enrolment time. There was no significant difference in suicidal behaviour between patients prescribed antibiotics only and those who were prescribed isotretinoin.

Although the results demonstrate a lower prevalence of suicidal behaviour in patients prescribed isotretinoin compared to the general population, an increase in suicidal behaviour after cessation of treatment among patients prescribed isotretinoin was observed. Because data collection starts 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.

The demonstrate that patients in the general population had significantly lower odds of having a psychiatric diagnosis compared to acne patients prescribed isotretinoin (adjusted OR = 0.87; 95% CI, 0.84-0.89; P<0.0001). These findings may reflect that acne is independently associated with low self-esteem and psychiatric conditions, such as depression and suicidal behaviour. Additionally, as acne patients undergoing treatment likely have more frequent contact with the health care system, it may be that they are more likely than the general population to be diagnosed with psychiatric disorders. These results showed patients prescribed antibiotics only had significantly lower odds of having a psychiatric diagnosis compared to those prescribed isotretinoin (adjusted OR, 0.88; 95% CI, 0.85-0.91; P<0.0001). It is possible greater severity of disease in the isotretinoin group may account for this trend, as acne severity has been correlated with an increased risk of psychiatric disturbances and social impairment.

Although patients with moderate to severe acne were more likely to have a psychiatric diagnosis when compared to the general population, they were less likely to be diagnosed with suicidal attempt or ideation. It is possible the increased prevalence of psychiatric diagnoses may be attributable to the impact of acne itself or increased patient contact with the health care system rather than the systemic medications used to treat acne. The lack of evidence suggesting an increased risk of suicide or suicidal ideation with isotretinoin treatment should provide reassurance to both patients and providers in prescribing isotretinoin. A medication-related effect in specific patients cannot be entirely ruled out, however, and it is reasonable to screen for depression-related symptoms at follow up visits while the patient remains on isotretinoin. Although suicide has long been a fear preventing more widespread appropriate isotretinoin prescription, this large cohort study does not support this concern.

Epidemiological Assessor's comments

The data source was based on insurance claims which would have excluded individuals who were uninsured or who have public insurance. The characteristics of the underlying populations are likely to differ across private and public health insurance plans and so may not be representative of the wider population.

The isotretinoin cohort consisted of patients who may have also been prescribed antibiotics prior to isotretinoin, although it isn't clear what proportion of the cohort this represented. There is therefore the potential for confounding by indication due to underlying acne severity.

The study outcomes were based on the prevalence of psychiatric diagnoses and the inclusion and exclusion criteria suggest patients were not excluded if they had a psychiatric diagnosis prior to the first prescription for isotretinoin or antibiotic. It is also unclear if there was a pre-specified risk window for measuring the AESIs (with the exception of suicidal behaviour) following the first prescription. Patients may therefore have already had an existing psychiatric diagnosis prior to starting treatment which would lead to bias.

Overall, whilst this study suggests isotretinoin is not associated with an increased risk of some psychiatric outcomes compared to antibiotics, there are numerous limitations which limit the ability to advance the understanding of the association between isotretinoin psychiatric risks.

Vona-Giralt G, Vilaplana-Carnerero C, Ouchi D, Gomez-Lumbreras A, Morros R, Giner-Soriano M. Risk of psychiatric events in women treated with isotretinoin: a self-controlled study with SIDIAP database. Expert Opin Drug Saf. 2023 Mar;22(3):213-219. doi: 10.1080/14740338.2022.2120608.

Aim

To assess the incidence of new psychiatric events in women receiving isotretinoin treatment.

Methods

This is a self-controlled population-based study including patients who were cases, those experiencing at least one psychiatric event and, who also acted as their own controls during the different periods of exposure and non-exposure to isotretinoin.

The study population included women of all ages from primary health care (PHC) centres with at least one prescription of isotretinoin during the period from 1 July 2014 to 31 December 2018. The data for the present study is derived from a previous SIDIAP (Information System for Research in Primary Care Catalan) data extraction for a study required by the European Medicines Agency, and included all women of childbearing potential (13–49 years-old) receiving treatment with oral retinoids (isotretinoin, alitretinoin, or acitretin) during the period indicated above in order to assess the changes in prescription and monitoring of these drugs after the update of the pregnancy prevention plan (PPP) in 2016. Women with part of their treatment episodes with isotretinoin outside the study period and those with a follow-up period that was less than 85% of the entire study period were excluded from the study.

Data were obtained from SIDIAP database, which captures anonymised clinical information from the 279 PHC centres, covering an approximate population of 5.8 million people from Catalonia, Spain. Data is entered by different HCPs and includes: socio-demographic data; anthropometric measures; health problems and conditions as captured by ICD-10 codes; visits to HCPs; specialist referrals;

clinical measures; alcohol and tobacco use; laboratory results; sick leave; prescription medications and their corresponding pharmacy invoice data and all-cause mortality.

The descriptive variables included were: age, MEDEA socioeconomic index, body mass index (BMI), smoking history, dermatological diagnoses, psychiatric diagnoses previous to the isotretinoin exposure, and psychotropic medication use previous to the isotretinoin exposure.

The independent (exposure) variable was the isotretinoin exposure during the study period. The isotretinoin exposure period was defined as the time period between the day of the first prescription and the last day of this prescription plus a risk exposure period of 30 days. All the time periods with no prescription of isotretinoin but occurring during the study period were classified as non-exposure periods, which could be previous or posterior to the isotretinoin exposure (Figure 1).

The dependent (outcome) variable was the occurrence of new psychiatric events, defined as any new psychiatric diagnosis and/ or a new psychotropic drug prescription during the study period, meaning not having any psychiatric event before the exposure period.

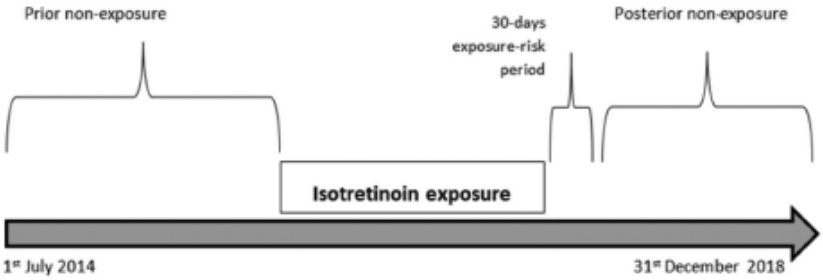


Figure 1. Isotretinoin exposure. The exposure period to isotretinoin was the time period between the day of the first prescription and the last day of this prescription plus a risk exposure period of 30 days.

Incidence rates (IR) per 1000 person-days of all psychiatric events, including diagnoses and prescriptions, were calculated for each period of exposure and non-exposure.

To estimate the association of a psychiatric event within both the exposure and non-exposure periods, Poisson-generalized linear mixed models (GLM) with the individual as a random effect were fitted. The results are expressed as Incidence Rate Ratio (IRR). In the multivariable model, the IRRs were adjusted by age at baseline and previous history of psychiatric conditions. Three GLM were fitted as follows:

1. the first to assess the first exposure period *vs.* the non-exposure period previous to isotretinoin exposure;
2. the second to compare the first exposure period *vs.* the non-exposure period posterior to isotretinoin exposure;
3. third to analyse the effect of having previous psychiatric diagnoses.

A subgroup analysis was conducted in the group of women who had not previously had a diagnosed of a mental disorder registered in the electronic health records (EHR).

Results

4,738 women were included in the study. They had a mean age of 23.2 (SD = 10.9) years of age and the primary documented indication for isotretinoin treatment was acne (84.6%). Of the total cohort, 1,200 (25.3%) had previous psychiatrics events (either diagnoses or psychotropic prescriptions); 941 (19.9%) had at least one psychiatric diagnosis documented in the EHR at the study initiation, with anxiety being the most frequently recorded condition (15.6%). A total of 847 (17.9%) females had

received at least one prescription for psychotropic drugs before the inclusion in the study, with anxiolytics and selective serotonin reuptake inhibitors (SSRI) as the most common medications (11% and 10.2%, respectively).

Overall, 14,126 episodes were analysed; 4,738 periods of isotretinoin exposure, 4,737 which were previous to exposure and 4,651 posterior to exposure. The length of observation for most individuals was between 100 and 500 days.

During the study period, 1,259 women experienced a new psychiatric event; 782 (16.5%) had an incident psychiatric diagnosis and 925 (19.5%) received a new psychotropic medication. The most frequent incident diagnosis was anxiety (46.3% of the events), and the most used treatments were anxiolytics and SSRI (39.7% and 36.4%, respectively), similar to the baseline exposure (Table 3).

Table 3. Incident psychiatric events during isotretinoin exposure.

Variables, n (%)	Women who had psychiatric events
Psychiatric diagnoses and/or psychotropic prescriptions	**N = 1259**
Psychiatric diagnoses during follow-up	**N = 782**
Anxiety	583 (46.3)
Bipolar disorders	19 (1.5)
Depression	113 (9.0)
Emotional alteration	35 (2.8)
Insomnia	117 (9.3)
Psychosis	11 (0.9)
Self-injurious behavior	16 (1.3)
Psychotropic drug prescriptions during follow-up	N = 925
Antidepressants, NMRI	150 (11.9)
Antidepressants, SSRI	458 (36.4)
Anxiolytics, benzodiazepine derivatives	500 (39.7)
Hypnotic and sedatives, benzodiazepine derivatives	96 (7.6)
Other antidepressants	140 (11.1)
Other psychotropic drugs	257 (20.4)

NMRI, nonselective monoamine reuptake inhibitors. SSRI; selective serotonin reuptake inhibitors.

With regards to the analysis of the risk of incident psychiatric events comparing the exposure and the previous non-exposure periods, the adjusted IRR was 1.12 (95% CI: 0.92–1.36). Using medications as marker of disease, the adjusted IRR was 1.12 (95% CI: 0.99–12.7). Neither finding was statistically significant (p-value > 0.05) (table 4).

The number of incident psychiatric diagnoses during the exposure as compared to after treatment cessation was also not statistically significantly based on diagnosis (IRR 0.87, 95% CI 0.72–1.07), or incident prescriptions (IRR 1.01, 95% CI 0.89–1.14). When the association of a psychiatric event in women with psychiatric history was analysed, the adjusted IRR for diagnoses was 1.60 (95% CI: 1.34–1.92) and for prescriptions it was 6.64 (95% CI: 5.32–8.29), suggesting that there was a higher probability of having new psychiatric event or medication after exposure to isotretinoin (p-values < 0.001) (table 4).

Table 4. Risk of incident psychiatric events during the exposure and non-exposure periods.

Incident psychiatric events during the exposure *vs* the previous non-exposure					
	Exposure	Previous non-exposure	IRR (95% CI)	Adj*IRR (95% CI)	p-value
N diagnoses	144	430	1.14	1.12	0.251
IR/1000 person-day	0.148	0.127	(0.93–1.38)	(0.92–1.36)	
N prescriptions	392	1105	1.13	1.12	0.076
IR/1000 person- day	0.404	0.325	(1.00–1.28)	(0.99–1.27)	
Incident psychiatric events during the exposure *vs* the posterior non-exposure					
N diagnoses	144	371	0.88	0.87	0.183
IR/1000 person-day	0.148	0.132	(0.72–1.08)	(0.72–1.07)	
N prescriptions	392	1190	1.01	1.01	0.926
IR/1000 person-day	0.404	0.424	(0.89–1.15)	(0.89–1.14)	
Incident psychiatric events during exposure in patients with psychiatric history *vs* no psychiatric history					
	No psychiatric history	Psychiatric history	IRR (95% CI)	Adj*IRR (95% CI)	p-value
N diagnoses	571	373	1.90	1.60	<0.001
IR/1000 person-day	0.107	0.204	(1.61–2.25)	(1.34–1.92)	
N prescriptions	833	1853	10.68	6.64	<0.001
IR/1000 person-day	0.156	1.011	(8.64–13.19)	(5.32–8.29)	

*Adjusted by age and previous psychiatric events before at the study inclusion.
IR; incidence rate. IRR; incidence rate ratio. CI; confidence interval.

A subgroup-analysis was conducted including those women with no history of psychiatric events, neither psychiatric diagnoses nor prescription of psychotropics (n = 3,538, 74.7%), obtaining lower IR/1000 person-day for diagnoses and prescriptions in the three periods studied in comparison with the main analysis. The adjusted IRR was significant for the prescriptions when we compared the exposure *vs* the previous non-exposure (IRR = 1.43, 95% CI 1.16–1.77, Table 5).

Table 5. Risk of incident psychiatric events during the exposure and non-exposure periods in women with no previous history of psychiatric disease.

Incident psychiatric events during the exposure *vs* the previous non-exposure				
	Exposure	Previous non-exposure	Adj*IRR (95% CI)	p-value
N diagnoses	89	246	1.28	0.0605
IR/1000 person-day	0.122	0.095	(1.00–1.65)	
N prescriptions	132	332	1.43	0.0012
IR/1000 person-day	0.181	0.128	(1.16–1.77)	
Incident psychiatric events during the exposure *vs* the posterior non-exposure				
	Exposure	Posterior non-exposure	Adj*IRR (95% CI)	p-value
N diagnoses	89	237	0.97	0.7669
IR/1000 person-day	0.122	0.117	(0.75–1.25)	
N prescriptions	132	370	1.13	0.2847
IR/1000 person-day	0.181	0.183	(0.91–1.42)	

IR; incidence rate. IRR; incidence rate ratio. CI; confidence interval.

Authors' conclusions

There was a high proportion of the patients who had been previously diagnosed or treated for psychiatric conditions (25.3%). This high frequency might be explained by the higher prevalence of mental disorders in people with severe acne, combined with the cohort only including women.

During follow-up, there was no increase of psychiatric events during the isotretinoin exposure periods in comparison with the non-exposure ones, however this may have been due to the lack of study power. The study did find any differences in the incidence of psychiatric events when we compared the exposure period with the posterior non-exposure.

With regards to the symptoms reported, the most frequent incident diagnosis was anxiety (46.3%) and the most frequent psychotropic drugs prescribed were anxiolytics (39.7%) and SSRI antidepressants (36.4%).

In the subgroup analysis including only patients with no psychiatric history, a lower incidence of psychiatric events was observed, supporting the results from the entire cohort, where there was an increase in the incidence of psychiatric events associated to the presence of previous mental disorders. It was not possible to ascertain if those previous mental disorders were associated to the acne diagnosis, as there have been reports of self-impaired self-image or depression and anxiety in people with severe acne in other studies.

The proportion of subjects with diagnosed depression in this study (9% of the psychiatric events) did not correspond to the proportion of antidepressants prescribed (36.4% for SSRI and 23% for other antidepressants). This could be to different reasons: depression is not always routinely registered in the PHC EHR, as found in previous studies, some antidepressants can also be used for different indications to depression. This is a limitation of the data, where medications are not linked to diagnoses. Another reason for the lack of concordance between diagnosis and medication use could be the social stigma associated with mental disorders. Another limitation of our the is that the population is only composed by women and this may affect the distribution of the psychiatric diseases found in this population.

Despite the lack of a significant relationship between acne and isotretinoin and psychiatric events, it is possible that for some individuals, receiving isotretinoin may precipitate a psychiatric event. The strength of this study is that it used a robust methodological approach by conducting a self-controlled case series. This design makes within-person comparison of event rates (either diagnosis or treatments) of the two periods (exposure and non-exposure) eliminating time-invariant confounding such as genetics and minimising some other confounding variables.

In conclusion, the study did show any association between acne and isotretinoin and new onset of psychiatric events in women of childbearing potential age.

Epidemiological Assessor's comments

This study was conducted in a cohort of women of child-bearing potential age and so the results may be generalisable to males.

The study grouped psychiatric diagnoses into a single composite outcome with no analyses conducted to evaluate the risk of specific psychiatric conditions. This could be due to a lack of power to conduct stratified analyses, but the use of a composite outcome makes the results difficult to interpret.

Whilst the study found a lower incidence of psychiatric events in patients with no previous psychiatric diagnosis, there was an increase in the incidence of psychiatric events in patients with a previous psychiatric diagnosis. It was not possible to determine if the previous mental health disorders with associated with an acne diagnosis or if the mental health events were recurrent and part of the same diagnosis.

Self-controlled case series (SCCS) study designs have the advantage of accounting for any factors or characteristics that remain constant over the observation period. However, SCCS are best suited to studying acute recurrent or non-recurrent events (Petersen et al, 2016). Some of the outcomes included in this study (e.g. anxiety, bipolar disorders, depression, insomnia and psychosis) may not be acute events or non-recurrent. The choice of study design to research this question is therefore questionable given the outcomes could be chronic and recurrent.

Overall, the limitations identified limit the ability to advance the understanding of the association between isotretinoin psychiatric risks.

References:

Petersen I, Douglas I, Whitaker H. Self controlled case series methods: an alternative to standard epidemiological study designs. BMJ 2016;354:i4515 http://dx.doi.org/10.1136/bmj.i4515.

Bremner JD. Isotretinoin and neuropsychiatric side effects: Continued vigilance is needed. J Affect Disord Rep. 2021 Dec;6:100230. doi: 10.1016/j.jadr.2021.100230

This literature review aimed to review reports of associations between isotretinoin and neuropsychiatric side effects, including depression, suicidal thoughts, suicide, mania, anxiety, impulsivity, emotional lability, violence, aggression, and psychosis. It was not described as a systematic review, and no meta-analysis was conducted.

The review combined a range of study and evidence types sourced from PubMed and PsycInfo, of which all but two were published prior to 2021. The two new studies (AlGhofaili, 2021; Droitcourt, 2021) are discussed in this assessment.

The authors conclude that the existence of neuropsychiatric side effects of isotretinoin is supported by the literature. They advise clinicians to warn all patients and family members of the possibility of neuropsychiatric side effects, and to carefully monitor patients over time, approaching patients with pre-existing or vulnerability to psychiatric conditions with caution.

Epidemiological Assessor's comments:

Overall, the paper is lacking detail in the methods of the literature review.

The search strategy is not provided, making it difficult to determine how comprehensive it was, whether relevant keywords were excluded, or how studies were selected for inclusion. No detail is provided on how data was extracted from identified studies, the number of reviewers, and how disagreements on data extraction and sources of bias were resolved. The review did not critically evaluate studies in terms of their strengths and limitations, no assessment of potential publication bias is included, and no results are presented.

The poor quality of the review, combined with only two studies post-2020 being included, means this review is unlikely to advance understanding of the association between isotretinoin and neuropsychiatric side effects.

Chandrasekaran S, De Sousa J, Paghdar S, et al. Is Isotretinoin in Acne Patients a Psychological Boon or a Bane: A Systematic Review. Cureus, 2021; 13(8): e16834. doi:10.7759/cureus.16834

This systematic review aimed to assess the relationship between isotretinoin and psychiatric side effects in acne patients.

A literature search was conducted using PubMed, Cochrane, and Google Scholar databases in accordance with Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines. Articles published within the last 10 years were taken into account and a review was conducted on the relevant articles after critical appraisal.

Nine studies were finalized for discussion and these two studies concluded that Isotretinoin could cause psychiatric effects. Five studies showed no association between them. Two studies unexpectedly found that psychiatric symptoms improved because of Isotretinoin use. Lack of adequate sample size and absence of randomized controlled trials were identified at limitations of the evidence available.

The authors concluded isotretinoin can be prescribed as a treatment option for severe acne despite some evidence of link with psychiatric effects. However, bearing the side effects in mind, a detailed

evaluation before initiating the drug and a thorough monitoring while using the drug should be done as a standard practice.

Epidemiological Assessor's comments

The methodology used to conduct the review appears to be broadly reasonable in line with best practise methodology. PubMed, Cochrane and Google Scholar were searched for literature published in the past 10 years with the review being conducted in 2021. The MeSH keywords were described but some additional relevant keywords could have been used, so there is the possibility some articles may have missed. Two authors independently assessed the articles for eligibility and extracted the data from the articles, although it is unclear what measures were in place if there was disagreement.

All papers were published pre-2021 in line with the other reviews therefore this review does not add any additional new evidence.

DeLuca M, Nuñez MB, Rodriguez E, Chirimunj K. Isotretinoin in Acne Vulgaris Complicated by Underlying Major Depression: A Case Report and Review of Literature. Case Rep Psychiatry. 2021 Jul 9;2021:9942327. doi: 10.1155/2021/9942327.

This literature review aimed to evaluate the evidence concerning the association between isotretinoin and increased suicidality. It was not described as a systematic review, and no meta-analysis was conducted.

The review included 14 studies, all of which were published prior to 2021.

The authors concluded that the incidence of suicidality may be no greater among individuals undergoing isotretinoin therapy than in the general population. They suggested that withholding therapy because of this potential association is not currently justified. Furthermore, they suggest that there is not sufficient evidence to discontinue isotretinoin in patients whose underlying root cause of major depressive disorder and suicidal ideation is identified as severe acne vulgaris, so long as a plan for consistent long-term monitoring and follow-up is in place.

Epidemiological Assessor's comments:

Overall, the paper is lacking detail in the methods of the literature review.

The search strategy is not provided, making it difficult to determine how comprehensive it was, whether relevant keywords were excluded, or how studies were selected for inclusion. No detail is provided on how data was extracted from identified studies, the number of reviewers, and how disagreements on data extraction and sources of bias were resolved. The review did not critically evaluate studies in terms of their strengths and limitations, no assessment of potential publication bias is included, and no results are presented.

The poor quality of the review, combined with no studies post-2020 being included, means this review is unlikely to advance understanding of the association between isotretinoin and increased risk of suicidality.

Fernandes T, Magina S. Oral isotretinoin in the treatment of juvenile acne and psychiatric adverse effects - a systematic review. Cutan Ocul Toxicol. 2023 Sep;42(3):83-90. doi: 10.1080/15569527.2023.2227889.

Aim

To determine if it is possible to establish a causal relationship between oral isotretinoin in the treatment of juvenile acne and the appearance of psychiatric adverse effects.

Methods

PubMed and Web of Science were searched for studies published between January 2000 and November 2021. Studies were included in the review if they focussed on adolescents and young adults up to 25 years taking oral isotretinoin for their acne. No restrictions were made when it came to severity of acne, previous use of oral isotretinoin, personal or family history of psychiatric disorders or psychiatric outcomes. Eligible studies included both randomised and nonrandomised controlled trials and observational studies while case reports and case series were excluded.

Two reviewers screened the titles and abstracts of potentially relevant articles. Any disagreements were resolved through discussion and final consensus. To assess the risk of bias in each study, two independent reviewers applied the Methodological Index for Non-Randomised Studies (MINORS) criteria.

Results

19 studies were included in the review and were all considered to have low to moderate bias according to MINORS criteria. One study was published in 2021 (AlGhofali, 2021) which has been included in this MHRA review. The remaining studies were all published prior to 2021.

Authors' conclusions

Overall, the review concluded the evidence considered does not suggest a causal relationship between oral isotretinoin and psychiatric side effects in adolescents and young adults.

Age was identified as a confounder due to the prevalence of acne in teenagers and young adults and mental disorders being more common during this period making it difficult to establish a causal link between isotretinoin and psychiatric disorders.

The authors advise the individual characteristics of each adolescent, and their environment should be considered; the personal and family history of mental disorders pointed out as red flags which should be identified when treating these patients. Patients should be questioned regarding the appearance of psychiatric side effects during every appointment as this is a vulnerable age group. Physicians should recognise that, although not common, behavioural changes can occur while on isotretinoin or after acne treatment with this drug, especially in patients with a psychiatric background and emotional frailty. More studies with larger populations and randomised controlled trials are necessary to increase the strength of evidence presented.

Epidemiological Assessor's comments

The methodology used to conduct the review appears to be broadly reasonable. PubMed and Web of Science were searched for literature published since 2000 with the review being conducted in 2022/23. The MeSH keywords were described but some additional relevant keywords could have been used, so there is the possibility some articles may have missed. Two authors independently assessed the articles for eligibility and extracted the data from the articles, with disagreement resolved by consensus.

Given the time period the review was conducted only one study was included which was published since 2021 (AlGhofaili, 2021 assessed in this MHRA review). The review is therefore unlikely to advance understanding of the association between isotretinoin and psychiatric adverse effects.

Annex B Yellow card data summary

Psychiatric disorders (SOC)

2019	Abnormal behaviour	1
	Aggression	4
	Agitation	2
	Anger	2
	Anhedonia	1
	Anorgasmia	3
	Anxiety	15
	Apathy	1
	Completed suicide	8
	Depersonalisation/derealisation disorder	2
	Depressed mood	7
	Depression	22
	Depression suicidal	2
	Depressive symptom	1
	Derealisation	1
	Insomnia	2
	Intentional self-injury	2
	Intrusive thoughts	1
	Irritability	3
	Libido decreased	7
	Loss of libido	5
	Mental disorder	4
	Mood altered	3
	Mood swings	1
	Neuropsychological symptoms	1
	Nightmare	2
	Obsessive-compulsive disorder	3
	Orgasmic sensation decreased	1
	Panic attack	3
	Paranoia	2
	Personality change	4
	Poor quality sleep	2
	Post-traumatic stress disorder	1
	Psychotic disorder	3
	Sleep disorder	1
	Social avoidant behaviour	2
	Stress	2
	Suicidal behaviour	1

	Suicidal ideation	18
	Suicide attempt	3
	Tearfulness	1
	Thinking abnormal	2
	Total	60
	Abnormal behaviour	1
	Affect lability	1
	Affective disorder	1
	Aggression	1
	Anger	4
	Anhedonia	2
	Anorgasmia	2
	Anxiety	10
	Apathy	1
	Bipolar disorder	2
	Completed suicide	11
	Confusional state	2
	Depressed mood	7
	Depression	17
	Depression suicidal	3
	Dissociation	1
	Eating disorder	3
	Emotional disorder	1
	Emotional distress	1
	Emotional poverty	1
	Euphoric mood	1
	Frustration tolerance decreased	1
2020	Generalised anxiety disorder	1
	Hallucination	2
	Hallucination, auditory	1
	Hallucination, olfactory	1
	Hallucination, tactile	1
	Hallucination, visual	1
	Impatience	1
	Insomnia	1
	Intentional self-injury	2
	Irritability	1
	Libido decreased	11
	Loss of libido	11
	Mania	2
	Mental disorder	2
	Mood altered	1
	Mood swings	6
	Negative thoughts	2
	Nightmare	1
	Obsessive thoughts	1
	Obsessive-compulsive disorder	3
	Panic attack	4
	Paranoia	4
	Personality change	1

	Psychotic disorder	3
	Shared psychotic disorder	1
	Sleep disorder	1
	Social avoidant behaviour	1
	Stress	1
	Suicidal behaviour	1
	Suicidal ideation	7
	Suicide attempt	4
	Taciturnity	1
	Tearfulness	1
	Thinking abnormal	1
	Total	68
	Aggression	2
	Agitation	1
	Anxiety	12
	Completed suicide	7
	Confusional state	1
	Depersonalisation/derealisation disorder	1
	Depressed mood	5
	Depression	15
	Depression suicidal	5
	Disturbance in sexual arousal	1
	Eating disorder	1
	Emotional distress	2
	Emotional poverty	1
	Fear	1
	Insomnia	3
	Intrusive thoughts	1
	Irritability	1
2021	Libido decreased	4
	Loss of libido	4
	Major depression	1
	Mania	1
	Mental disorder	1
	Merycism	1
	Mood altered	1
	Nightmare	2
	Obsessive-compulsive disorder	2
	Personality change	1
	Psychiatric symptom	1
	Psychotic disorder	7
	Stress	1
	Suicidal behaviour	1
	Suicidal ideation	10
	Suicide attempt	3
	Thinking abnormal	1
	Total	53
	Aggression	1
2022	Anger	1
	Anhedonia	2

	Anorgasmia	2
	Anxiety	12
	Apathy	2
	Blunted affect	1
	Bradyphrenia	1
	Completed suicide	1
	Depersonalisation/derealisation disorder	1
	Depressed mood	4
	Depression	10
	Depression suicidal	2
	Emotional poverty	1
	Insomnia	4
	Irritability	1
	Libido decreased	6
	Loss of libido	15
	Male orgasmic disorder	1
	Panic attack	2
	Personality disorder	1
	Poor quality sleep	1
	Psychogenic erectile dysfunction	1
	Rebound psychosis	1
	Sleep talking	1
	Somnambulism	1
	Suicidal ideation	7
	Suicide attempt	1
	Total	46
2023	Abnormal dreams	1
	Aggression	2
	Anxiety	6
	Apathy	2
	Binge eating	1
	Completed suicide	2
	Depressed mood	5
	Depression	8
	Depression suicidal	1
	Feelings of worthlessness	1
	Hallucination	1
	Hallucination, auditory	2
	Hallucination, visual	1
	Loss of libido	4
	Major depression	2
	Mental disorder	2
	Mood swings	3
	Obsessive-compulsive disorder	1
	Psychotic disorder	1
	Self-injurious ideation	1
	Sleep terror	1
	Suicidal behaviour	1
	Suicidal ideation	8
	Suicide attempt	4

2024	Suicide threat	1
	Total	38
	Abnormal dreams	1
	Acute psychosis	1
	Adjustment disorder with depressed mood	1
	Anxiety	4
	Apathy	1
	Completed suicide	1
	Delusion	1
	Depressed mood	2
	Depression	8
	Hallucination	1
	Insomnia	3
	Intrusive thoughts	1
	Libido decreased	5
	Loss of libido	11
	Mania	1
	Mood altered	1
	Mood swings	2
	Orgasmic sensation decreased	1
	Personality change	1
	Premature ejaculation	1
	Psychotic disorder	3
	Schizotypal personality disorder	1
	Self-injurious ideation	1
	Sleep disorder	1
	Somniphobia	1
	Suicidal ideation	5
	Suicide attempt	1
	Tic	2
	Time perception altered	1
	Total	38

Reproductive system and breast disorders (SOC)

2019	Adnexa uteri pain	1
	Ejaculation disorder	2
	Erectile dysfunction	18
	Genital hypoaesthesia	2
	Gynaecomastia	1
	Heavy menstrual bleeding	2
	Hypomenorrhoea	1
	Intermenstrual bleeding	1
	Male sexual dysfunction	1
	Menstruation delayed	1
	Menstruation irregular	1
	Sexual dysfunction	3
	Vulvovaginal dryness	2

	Total	28
2020	Amenorrhoea	3
	Erectile dysfunction	13
	Genital hypoaesthesia	1
	Male sexual dysfunction	1
	Sexual dysfunction	1
	Vulval disorder	1
	Vulvovaginal dryness	1
2021	Total	19
	Amenorrhoea	2
	Dyspareunia	1
	Erectile dysfunction	7
	Female sexual dysfunction	1
	Genital hypoaesthesia	1
	Hypomenorrhoea	1
	Infertility	1
	Male sexual dysfunction	1
	Menstrual disorder	1
	Menstruation delayed	1
	Nipple pain	1
	Perineal pain	1
	Premature menopause	1
	Sexual dysfunction	5
	Vulvovaginal dryness	1
	Vulvovaginal pain	1
2022	Total	20
	Dyspareunia	2
	Erectile dysfunction	14
	Female sexual dysfunction	1
	Genital anaesthesia	2
	Genital atrophy	1
	Gynaecomastia	1
	Heavy menstrual bleeding	1
	Intermenstrual bleeding	1
	Male sexual dysfunction	2
	Menstruation delayed	1
	Menstruation irregular	1
	Organic erectile dysfunction	2
	Sexual dysfunction	4
	Testicular pain	1
	Vaginal haemorrhage	1
	Vulvovaginal dryness	4
2023	Total	28
	Amenorrhoea	1
	Erectile dysfunction	13
	Genital burning sensation	1
	Gynaecomastia	4
	Heavy menstrual bleeding	1
	Male sexual dysfunction	2
	Menstruation delayed	1

	Menstruation irregular	4
	Vulvovaginal dryness	3
	Total	29
2024	Amenorrhoea	1
	Dysmenorrhoea	1
	Ejaculation delayed	3
	Erectile dysfunction	10
	Genital anaesthesia	2
	Heavy menstrual bleeding	1
	Hypomenorrhoea	1
	Male sexual dysfunction	1
	Menstrual disorder	2
	Penis disorder	1
	Sexual dysfunction	6
	Vaginal discharge	1
	Vaginal odour	1
	Vulvovaginal dryness	2
	Total	28