

Acne and Acne treatments

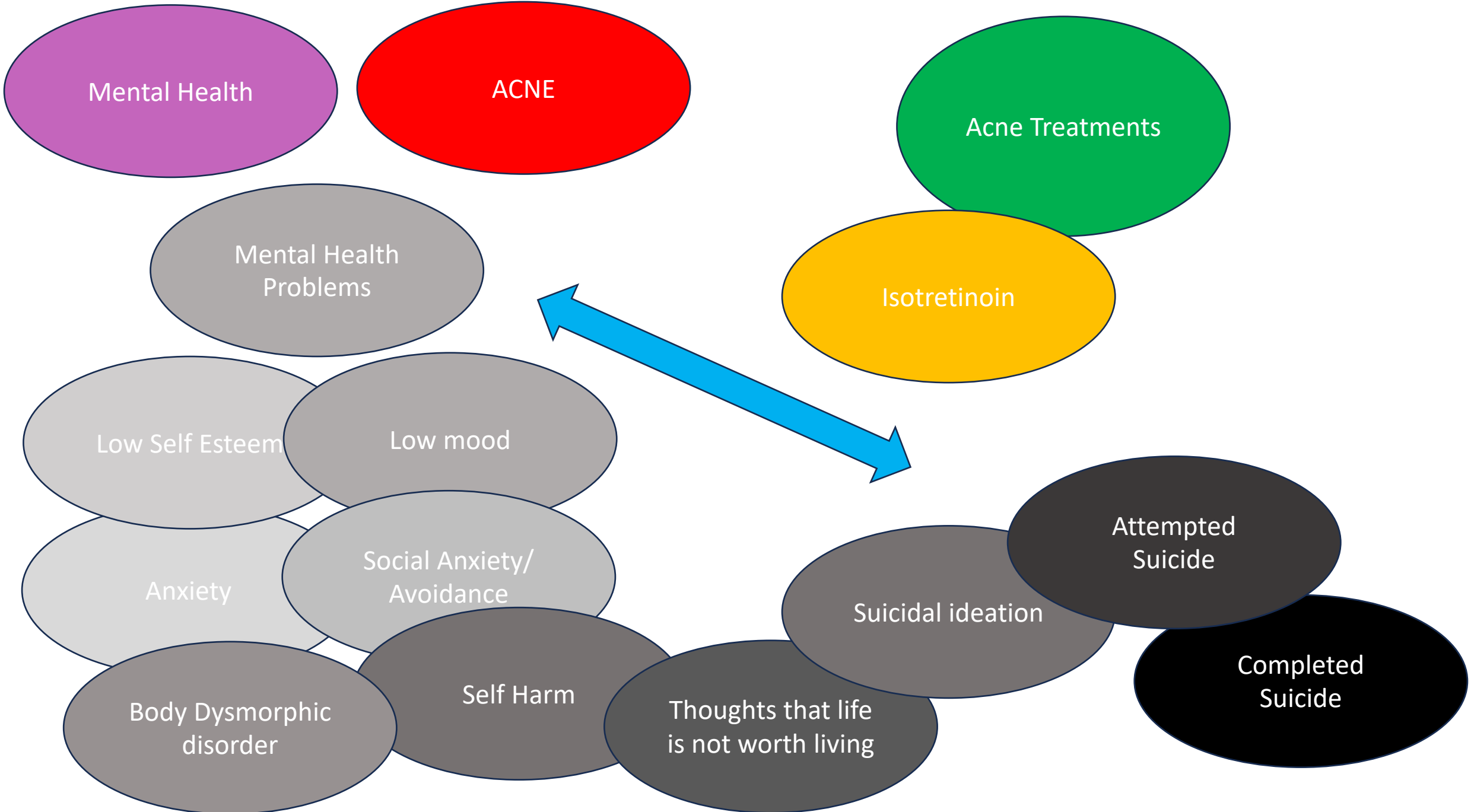
Evidence of impact on mental health and suicide risks
Nottingham EBM Update May 2024

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Disclosures

- Recent BSPAD president and BSPAD mental health working group
- Implementation MHRA guidance and Isotretinoin BAD working group
- Educational speaker fees and conference attendance supported by:
 - AbbVie, Sanofi, Leo, Pfizer, Janssen, Novartis, La Roche-Posay, Galderma



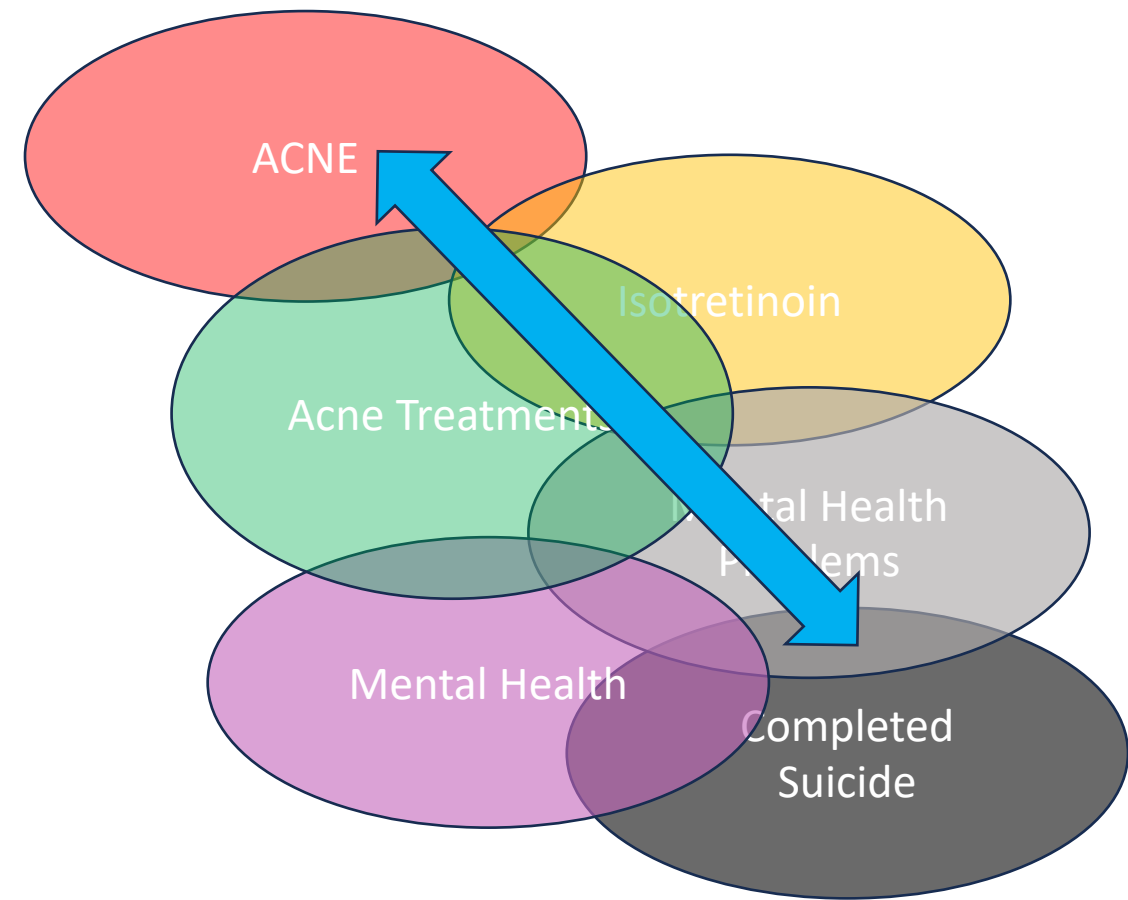
Evidence based update

Acne and Acne Treatments

Evidence of impact on mental health and suicide risks

Evidence base?

- Expert Opinion
- Clinical experience
- Case studies
- National data sets
- Yellow card reports
- Retrospective case series
- Prospective case series
- Systematic reviews



Young people – a time of significant mental ill-health



Mental ill-health at age 17 in the UK

Prevalence of and inequalities in psychological distress, self-harm and attempted suicide

The past decade or so has seen a growing policy focus on young people's mental health, with governments repeatedly stating their commitment to improving prevention and access to mental health services for young people. Three-quarters of lifetime mental illness are first experienced before age 20¹, highlighting that prevention efforts in the first two decades of life are vital. There are also stark differences in the experience of common mental health difficulties across young people, with important implications for inequalities in a host of social, economic and health outcomes later on.

This report focuses on mental ill-health at age 17, using data collected from participants in the Millennium Cohort Study (MCS) in 2018-19. It presents prevalence of psychological distress, self-harm and attempted suicide. It describes important mental health inequalities across the following key socio-demographic characteristics: sex, ethnicity, sexuality and socioeconomic position.

Combined with data collected from a subset of participants during the COVID-19 national lockdown in May 2020, when they were aged 19, the report also presents evidence on changes in psychological distress from ages 17 to 19.

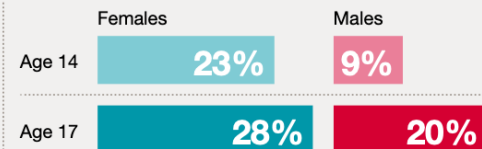
Key findings

- High levels of severe mental health difficulties:** The prevalence of high psychological distress is 16.1% (95% CI: 14.7, 17.7), 12-month prevalence of self-harm is 24.1% (95% CI: 22.6, 25.7) and lifetime attempted suicide is 7.4% (95% CI: 6.6, 8.3).
- Large inequalities:** Females, White adolescents, sexual minorities and those from lower income households have poorer mental health across most outcomes. The exceptions are: no ethnic differences in attempted suicide and no socioeconomic differences in self-harm.
- Stark sex differences:** Prevalences of mental health difficulties are consistently higher among females than males: 22.1% of females and 10.1% of males experienced high psychological distress, 28.2% of females and 20.1% of males self-harmed and 10.6% of females and 4.3% of males attempted suicide.
- Increased risk among sexual minority adolescents:** There are stark inequalities by sexuality, with over half (55.8%) of LGB+ young people reporting self-harming in the last year and 21.7% of LGB+ young people having attempted suicide.

Increase in prevalence of self-harming between ages 14 and 17

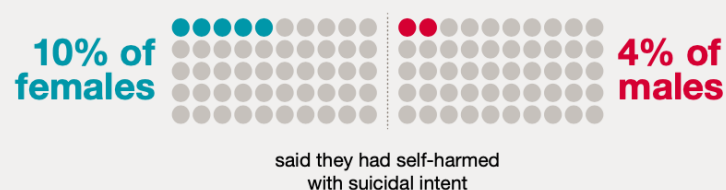
1 in 4

teenagers reported self-harming in past 12 months, with rates increasing since study members were last surveyed at age 14



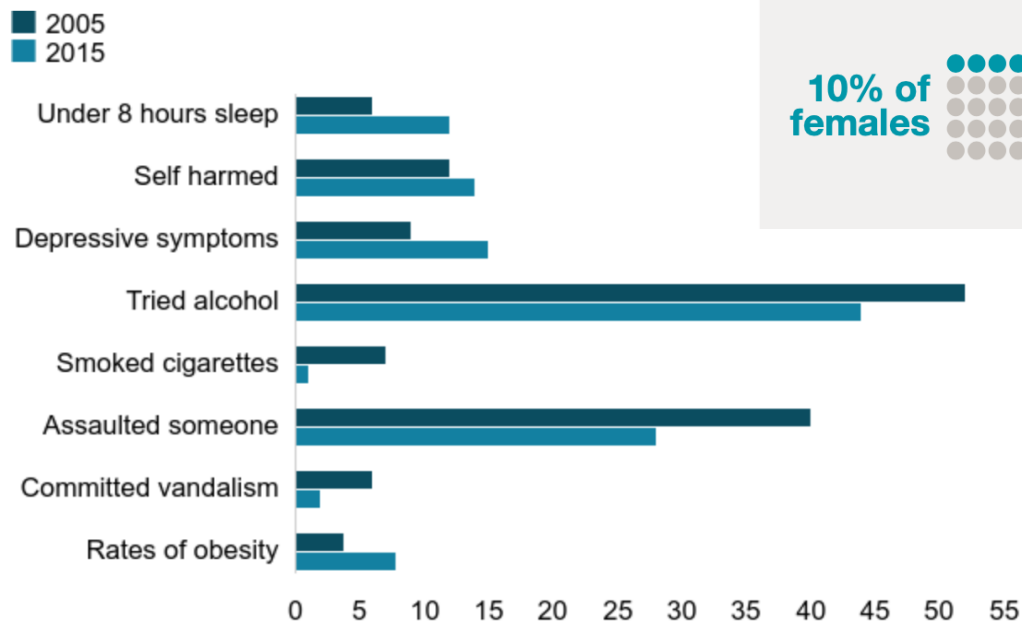
Prevalence of attempted suicide

By age 17, approximately



How the health and behaviour of teenagers changed over 10 years, 2005-15

Study based on two surveys of 14-year-olds



Source: Patalay and Gage, International Journal of Epidemiology



By Praveetha Patalay and Emla Fitzsimons
NOVEMBER 2020

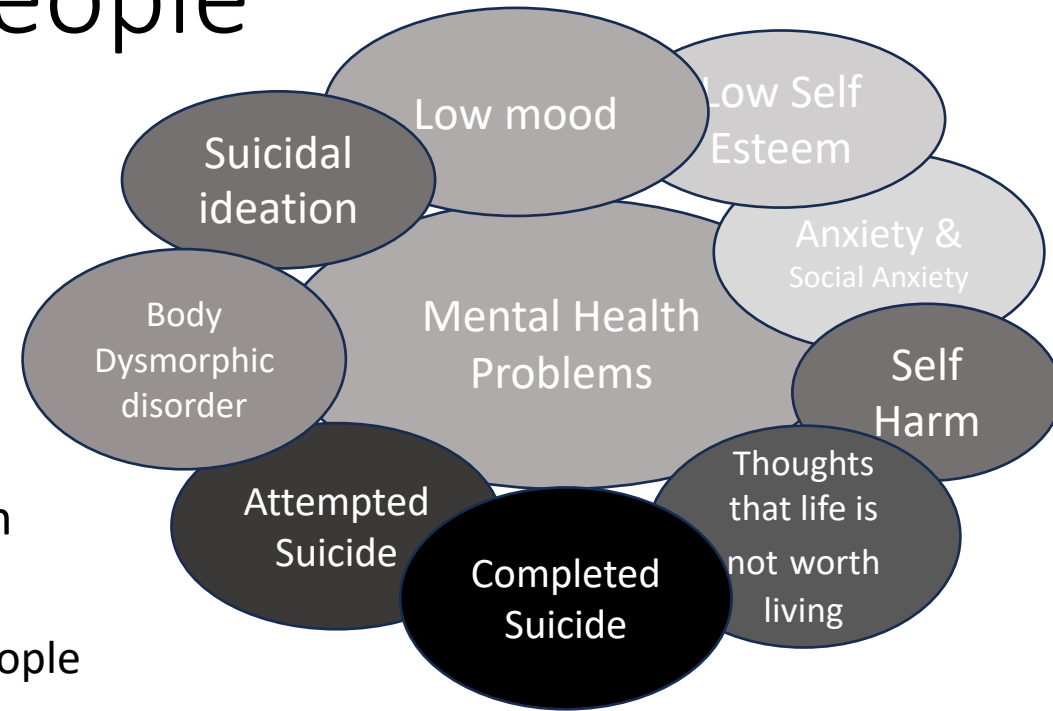
CENTRE FOR LONGITUDINAL STUDIES



Poor mental health in young people Spectrum but not linear

- Low mood
 - risk factor for self harm, suicidal ideation, attempted suicide, suicide
- Self harm = risk factor for suicide but can be coping mechanism
- 'Suicidal ideation' – active vs passive
 - Thoughts that life is not worth living = very common in young people
 - Feeling you would rather be dead +/- plans
 - Attempted suicide = can be cry for help rather than wish to die

Asking about suicidal thoughts does NOT make suicide more likely

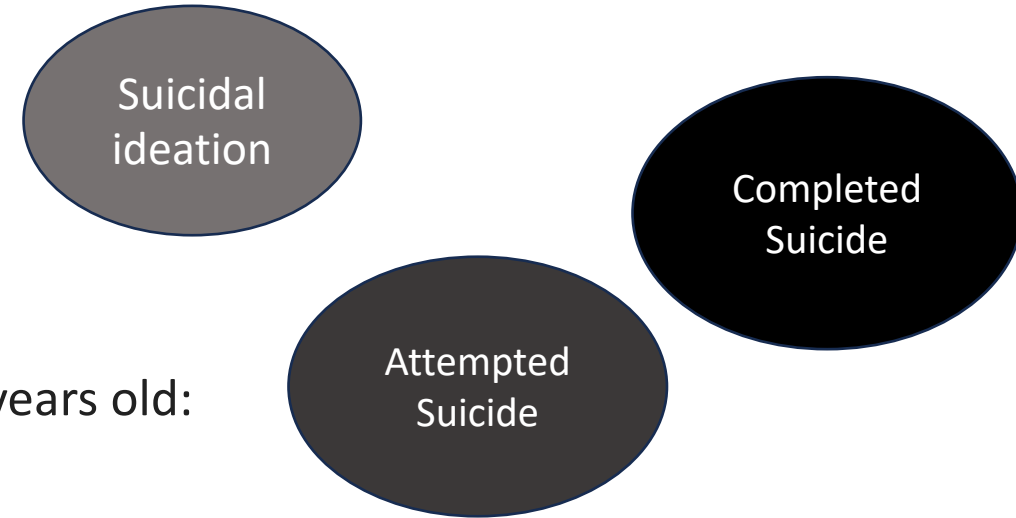


Klonsky ED, May AM, Saffer BY. Suicide, Suicide Attempts, and Suicidal Ideation. Annu Rev Clin Psychol. 2016

Harmer et al Suicidal ideation 2023

Dazzi T, et al Does asking about suicide and related behaviours induce suicidal ideation? What is the evidence? Psychol Med. 2014

Suicide in young people



- Suicidal behaviour is comparatively high in adolescents at 18 years old:
 - Suicidal ideation 22.5%
 - Suicidal attempts 5.2%

Fergusson DM et al Risk factors and life processes associated with the onset of suicidal behaviour during adolescence and early adulthood. Psychol Med 2000

- Completed suicide
 - USA mortality 2017 >50% of deaths by suicide people with no known psychiatric illness
 - UK data similar for young people
 - Data that people who completed suicide had denied intentions in most recent hospital visit
 - Concerning increase in young people completing suicide globally
 - 2nd leading cause of death in 15-30 in 2016
- Completed Suicide remains rare – makes studying risk particularly difficult
- Every suicide is a tragedy – people want answers

Annabel Wright: Acne drug link to Ripon teen's suicide ruled out

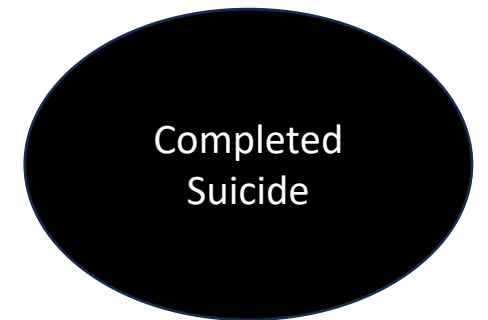
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FAMILY PHOTO

Suicide in young people – predictors

- 3-year UK national mortality data 2014-16 deaths by suicide age 10-19
- Antecedent data from official investigations primarily inquests
 - 595 suicides in young people (almost 200 per year)
 - 71% male (n=425)
 - Most in age 17-19 (n=443 74%)
 - Data for antecedents for 544 (91%)
 - Witnessing domestic violence
 - Bullying
 - Self harm
 - bereavement (including by suicide)
 - Academic pressure (girls > boys)
 - Drug misuse (boys > girls)
 - 329 (60%) had been in contact with specialist children's services 40% had not been



Acne and Mental health

- Does poor mental health cause Acne?
 - Some evidence that stress can make acne worse in susceptible people
- Is Acne associated with poor mental health? **YES**
 - Much evidence of the link with skin disorders and impact on mental health
 - Increased in patients with acne and acne scarring compared with people without acne:
 - Low mood
 - Social anxiety
 - Self harm
 - Body dysmorphic disorder
 - Thoughts that life is not worth living
 - Suicide
 - Causality- Strong evidence backed by qualitative data and clinical experience



Why?

- Symptoms - Painful
- Visible and hidden skin difference (eg back acne)
- Society stigma – people with acne are judged as less attractive , less healthy, less employable
- Short term and long-term impact (scarring can be physical and emotional)

The impact of skin disease on teenagers self esteem

during this age can be 'devastating' UK All Parliamentary Group - Skin and Mental health 2020

Evidence for Acne links with Suicide behavior/ ideation

1/7

REVIEW ARTICLE

Suicide and Suicidality in Children and Adolescents with Chronic Skin Disorders: A Systematic Review

Richard BARLOW¹, Girija PAYYAZHI², Sarah HOGAN³, Dougal GRINDLAY⁴, Donald CHOI³, Meenakshi VERMA³, Kavitha PASUNURU⁵, Ruth TAYLOR³, Anthony BEWLEY³ and Padma MOHANDAS³

¹University Hospital Coventry and Warwickshire, Coventry, ²Cardiff and Vale University Health Board, Cardiff, ³Royal London Hospital, London ⁴Centre of Evidence Based Medicine, Nottingham, and ⁵Aneurin Bevan University Health Board, Aneurin Bevan

New Zealand 9567 secondary school students aged 12-18 years

- Self-reported 'problem acne' no info on treatment)
- Controlling for co-existent depression and anxiety
- Suicidal behaviour = Odds ratio (OR) 1.5 (95% CI) 1.21–1.86) cw those without acne

(Purvis et al, 2006)

Cross-sectional study people with self-reported mild-to-moderate acne, mean age 23

- Prevalence of suicidal ideation = 5.6%

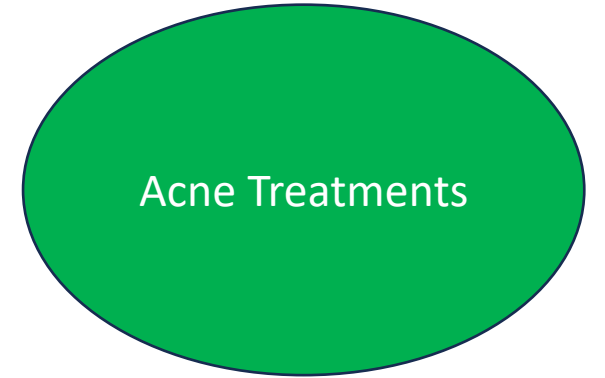
(Gupta et al 2000)

Male military conscripts Finland aged 18–25 years old with acne (n=165)

- No significant increase in comorbid psychopathology including suicidal ideation compared to controls (n=150)

(Rehn et al JEADV 2008)

Acne treatments and mental health Questions?



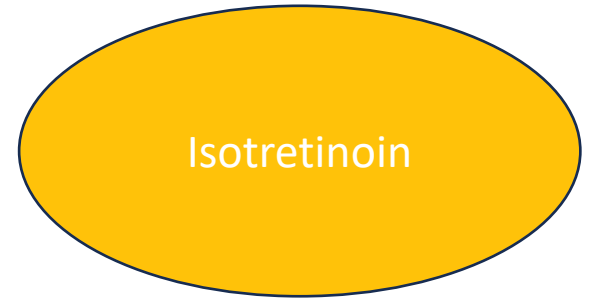
- Do treatments improve acne?
- Do treatments that improve acne improve mental health?

- Can treatments cause mental health problems?
- How do we prove causality?

Background – Isotretinoin

- Isotretinoin 13 cis-retinoic acid therapy
- First approved in 1980s
- Prescribed to around 50,000 people a year in UK

- Now taken by millions of people
- Most effective treatment for acne
- Sustained impact in many
- Side effects in majority predictable – mucositis, photosensitivity
 - Need for pregnancy prevention



Acne treatments and mental health: Isotretinoin

- Isotretinoin is effective to treat acne (Network Meta Analysis/ NICE guidance)

Questions:

- Does Isotretinoin cause mental health problems?
- Does Isotretinoin improve mental health?
- Can causality be proven?

- This has been and is still a contentious issue ..

Depression—a side effect of 13-*cis*-retinoic acid therapy

To the Editor:

Reported side effects of 13-*cis*-retinoic acid (isotretinoin) have included cheilitis, xerosis, skin fragility, bone aching, headache, stomach upset, alopecia, and corneal abnormalities.¹ We now wish to report another side effect recently observed by us—depression.

Six of 110 patients (5.5%) with acne or keratinizing disorders treated with 1.0 to 2.0 mg/kg body weight/day experienced depressive symptoms while on the drug. The depression was present in five patients with acne and in a single patient with palmar-plantar keratoderma associated with hypohidrotic ectodermal dysplasia. Four patients were women and two were

men. The mean age of affected patients was 28.5, with a range from 20 to 42 years. One patient had a previous history of depression. In a 21-year-old man, symptoms of depression and forgetfulness were severe enough to cause withdrawal of the drug. The other five patients continued with the drug despite feelings of depression.

All patients experienced depressive symptoms, manifested by crying spells (3/6), malaise (3/6), or forgetfulness (1/6), within 2 weeks of starting the drug. Symptoms rapidly resolved on discontinuing the drug.

Meyskens² noted similar psychologic changes in patients with cancer treated with 3 mg/kg/day of 13-*cis*-retinoic acid. Peck,³ however, saw psychologic improvement in his patients with acne treated with isotretinoin. It was not reported whether any of their patients had a previous history of psychiatric disorder.

Paul G. Hazen, M.D.

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Hazen PG, Carney JF, Walker AE, Stewart JJ. Depression—a side effect of 13-*cis*-retinoic acid therapy.

J Am Acad Dermatol. 1983

REFERENCES

1. Windhorst DB, Nigra T: General clinical toxicology of oral retinoids. J AM ACAD DERMATOL 6:675-682, 1982.
2. Meyskens FL Jr: Short clinical reports. J AM ACAD DERMATOL 6:732, 1982.
3. Peck GL: Short clinical reports. J AM ACAD DERMATOL 6: 732-733, 1982.

Mechanistic theories – Isotretinoin-Neuropsychiatric

- Large amounts of vitamin A known to be neurotoxic
- Isotretinoin does cross the blood-brain barrier
- Receptors for retinoids are widely expressed in brain
- Isotretinoin could potentially regulate the expression of several neuronal genes
- Functional brain imaging showed decreased brain metabolism following isotretinoin cw antibiotics (Brenner 2005)
- Mouse models – behavioural change with chronic administration of 13-cis-RA (O-Reilly 2006)
- Some evidence for retinoid class effect

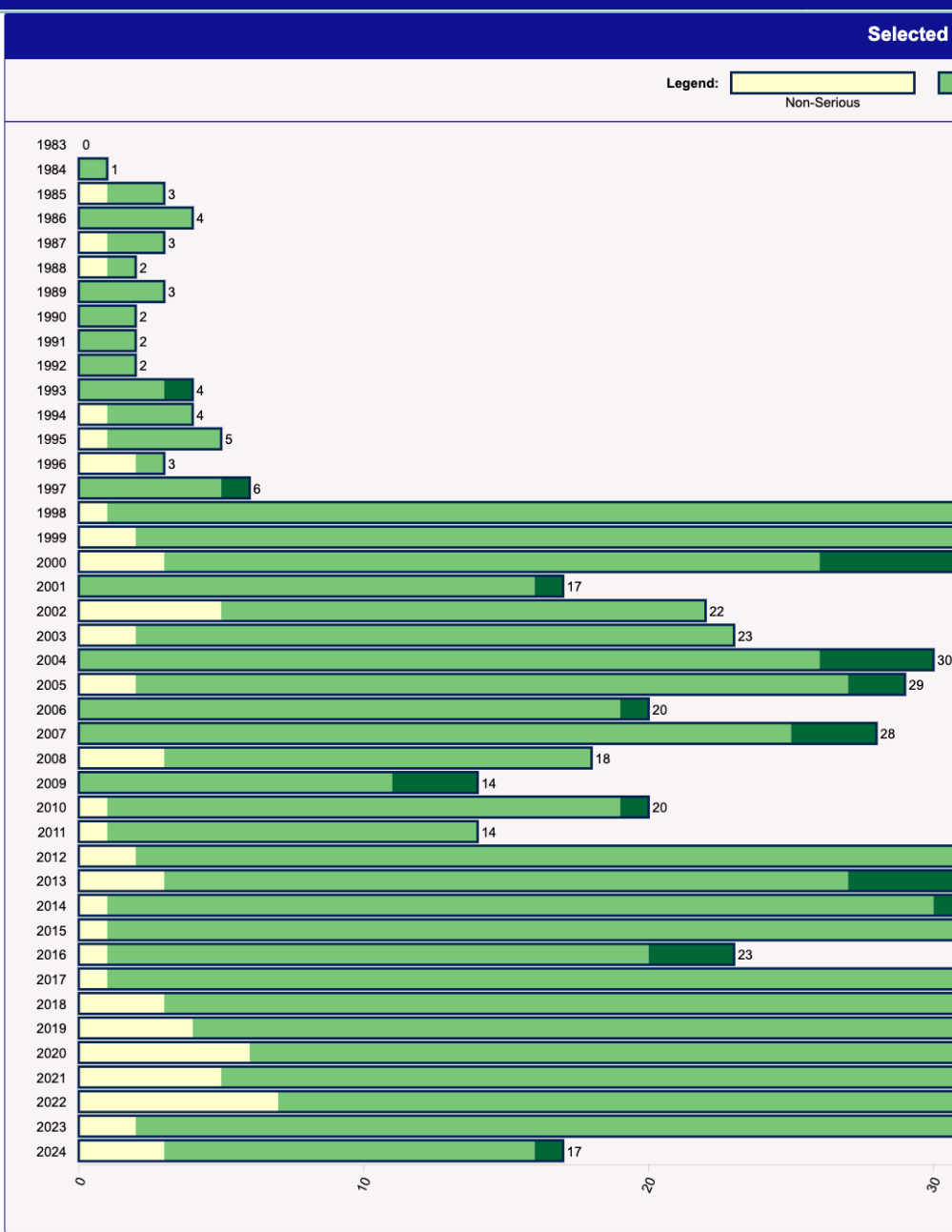
- However-
- No impact on serotonin 5HT 5H1AA in recent prospective small study (Bray et al 2022)

- ALSO - Important to consider impact of common somatic & neurological side effects
 - Headache relatively common reported side effect (and Benign intracranial hypertension)
 - bidirectional association between headache and depression
 - co-occurring headache and depression reported in patients on isotretinoin

Yellow card scheme

- Developed in 1964
- Response to thalidomide – 1950s
 - Association with limb deformities not seen in clinical trials
 - No data on pregnant women yet marketed as ‘completely safe’
- UK system for collecting information on suspected adverse drug interactions to medicines and vaccines
- Any suspected Adverse Drug Reaction – encouraged to report
- Originally just for doctors
 - Extended to pharmacists in the late 1990s
 - Now open to members of the public – since 2010s

- Neoplasms benign, malignant and unspecified (incl cysts and polyps)
- Nervous system disorders
- Pregnancy, puerperium and perinatal conditions
- Product issues
- Psychiatric disorders
- Renal and urinary disorders
- Reproductive system and breast disorders
- Respiratory, thoracic and mediastinal disorders
- Skin and subcutaneous tissue disorders
- Social circumstances
- Surgical and medical procedures
- Vascular disorders



Psychiatric disorders	1955	85	6	0	1960	85
Adjustment disorders (incl subtypes)	5	0	0	0	5	0
Anxiety disorders and symptoms	258	0	1	0	258	0
Changes in physical activity	2	0	0	0	2	0
Cognitive and attention disorders and disturbances	3	0	0	0	3	0
Communication disorders and disturbances	3	0	0	0	3	0
Deliria (incl confusion)	23	0	0	0	23	0
Dementia and amnesic conditions	1	0	0	0	1	0
Depressed mood disorders and disturbances	568	0	3	0	571	0
Developmental disorders NEC	1	0	0	0	1	0
Dissociative disorders	8	0	0	0	8	0
Disturbances in thinking and perception	73	0	0	0	73	0
Eating disorders and disturbances	12	0	0	0	12	0
Impulse control disorders NEC	1	0	0	0	1	0
Manic and bipolar mood disorders and disturbances	19	0	0	0	19	0
Mood disorders and disturbances NEC	189	0	0	0	189	0
Personality disorders and disturbances in behaviour	122	0	0	0	122	0
Psychiatric and behavioural symptoms NEC	24	0	0	0	24	0
Psychiatric disorders NEC	25	0	1	0	26	0
Schizophrenia and other psychotic disorders	74	0	0	0	74	0
Sexual dysfunctions, disturbances and gender identity disorders	126	0	0	0	126	0
Sleep disorders and disturbances	65	0	0	0	65	0
Somatic symptom and related disorders	2	0	0	0	2	0
Suicidal and self-injurious behaviours NEC	351	85	1	0	352	85

Yellow card reports on Isotretinoin in UK 2019-2023



Suicides in UK patients on isotretinoin

- Suicide total: **83**
- Suicides 2019: **8** (5,316 nationally)
- Suicides 2020: **12** (5,244 nationally)
- Suicides 2021: **9** (5,583 nationally)
- Suicides 2022: **1** (5,275 nationally)
- Suicides 2023: **1**

Side effect class

- **Psychiatric** **1914**
- Skin and subcutaneous 863
- Gastro-intestinal 809
- Neuro (headache) 585
- Musculoskeletal 516
- Eye 422
- **Sexual dysfunction** **291**
- **Pregnancy related** **167**
- Blood abnormalities 122

Thanks to Jane Ravenscroft

nb isotretinoin prescribed ~50,000 per year in UK = 250,000 people:
estimated reported frequencies: Psychiatric se 1914= 0.008%, Sexual function se 291= 0.001%

Evidence ...

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

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

Comment received through call for information

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

Comment received through call for information

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

Comment received through call for information

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

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

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

Comment received through call for information

whether isotretinoin was suitable for younger

Independent report

REPORT OF THE COMMISSION ON HUMAN MEDICINES ISOTRETINOIN EXPERT WORKING GROUP

26 April 2023

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

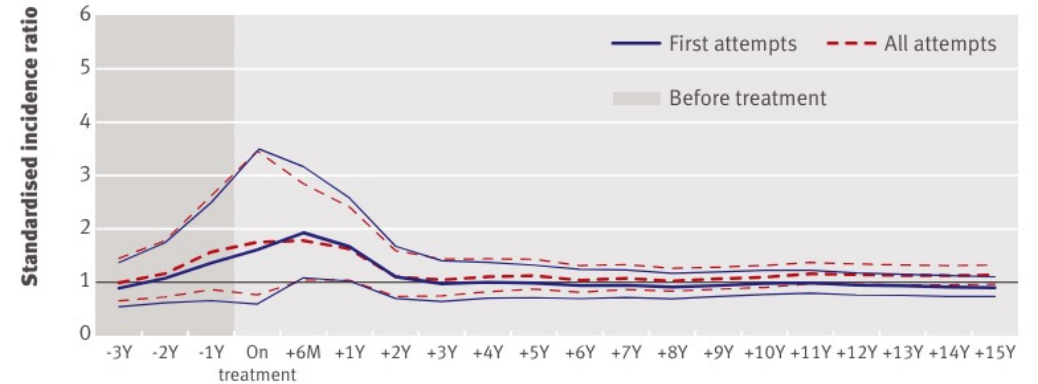
- To evaluate information from all available sources, including relevant stakeholders (patients, patient representatives, healthcare professionals, healthcare organisations, researchers, charity and patient organisations) on psychiatric effects suspected to be associated with isotretinoin. To consider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

Association of suicide attempts with acne and treatment with isotretinoin: retrospective Swedish cohort study

Anders Sundström, pharmacoepidemiologist,^{1,2,3} Lars Alfredsson, professor in epidemiology,⁴ Gunilla Sjölin-Forsberg, dermatologist and clinical pharmacologist,² Barbro Gerdén, dermatologist, senior expert,² Ulf Bergman, clinical pharmacologist,³ visiting professor,¹ Jussi Jokinen, senior psychiatrist⁵

BMJ 2010 - Retrospective study

- 5756 age 15-49 prescribed Isotretinoin in Sweden 1980-2001
- 128 admitted to hospital for **attempted suicide**
- 24 completed suicide
- Report increased risk of attempted suicide increased before treatment and up to a year after Isotretinoin treatment completed compared with expected numbers (national data)
- OR 1.78 (1.04-2.85) for all attempts
- OR 1.93 (1.08- 3.18) for first attempts
- Highest risk was in 6 months after started treatment (only point of statistical significance)
- 3 years after treatments report close to expected rate (? Due to effective treatment)



Cumulative No

First	20	16	10	6	15	20	22	28	37	44	49	56	60	68	77	84	86	90	92	94
All	27	21	14	8	17	24	28	38	52	65	71	85	92	106	119	136	143	149	155	161

Fig 1 | Standardised incidence ratios for accumulated first suicide attempts and all attempts from up to three years before (shaded area) to up to 15 years after treatment in all patients. Thin lines show 95% confidence intervals

WHAT IS ALREADY KNOWN ON THIS TOPIC

Case reports and spontaneous reports of adverse drug reactions have suggested an association between isotretinoin and suicidal behaviour, but observational studies have had conflicting results

Isotretinoin has been shown to have behavioural effects in mice and effects on cerebral metabolism in humans

WHAT THIS STUDY ADDS

Severe acne is a risk factor for attempted suicide; an additional risk may be present during and up to one year after treatment with isotretinoin

Suicidal behaviour triggered during isotretinoin treatment more often leads to repeated attempts or suicide than in patients with a history of suicide attempts before treatment

A history of attempted suicide may not need to be a contraindication when considering treatment with isotretinoin

Routine data set USA

BJD 2022

123,414 patients with acne age 12-27

- 30866 isotretinoin cohort
- 108367 topical antiacne agents cohort
- 44748 oral antibiotics cohort
- 78666 in the cohort of acne patients without antiacne prescription medicines

Main findings

- Mental health issues common - 7-10% of patients with acne diagnosed mood disorder such as clinical depression
- After propensity score-matching for baseline confounders incident neuropsychiatric outcomes in patients exposed to isotretinoin for 1 year.

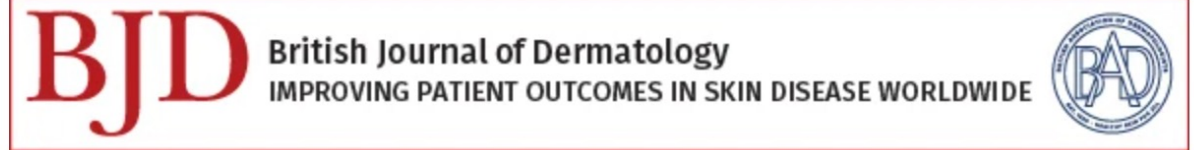
Isotretinoin medication was unlikely causing poor mental health in patients prescribed Isotretinoin for acne.

Isotretinoin seemed to modify the impact of acne on mental health

No data on cause of death (suicide). No significant difference in deaths but very low numbers (19 vs 12)

People who took isotretinoin medication had slightly better mental health than those who took oral antibiotic medication for acne

Reduced rate of conditions such as anxiety, depression, sleep problems, non-fatal self-harm, and prescriptions for medications such as anti-depressants.



Epidemiology | [Open Access](#) |

Isotretinoin and adverse neuropsychiatric outcomes: retrospective cohort study using routine data

Tapio Paljarvi, Tess McPherson, Sierra Luciano, Kimmo Herttua, Seena Fazel

What does this study add?

- After controlling for various potential sources of bias, isotretinoin was associated with a reduced incidence of adverse psychiatric outcomes (odds ratio 0.80, 95% confidence interval 0.74–0.87) compared with oral antibiotics.
- Isotretinoin appeared to reduce the excess psychiatric risk associated with treatment-resistant moderate-to-severe acne.
- In monitoring potential adverse outcomes during isotretinoin treatment, clinicians should also consider the high mental health burden associated with treatment-resistant acne and the potential contribution of physical side-effects of the prescribed medication on mental health.

Now - 2024- Data for age 12-17 *In press JAAD*

42,334 Young people with Acne
21,167 isotretinoin.

Isotretinoin treatment not independently associated with increased 1-year incidence of neuropsychiatric diagnoses compared to treatment with oral antibiotics in pediatric acne patients.

Isotretinoin treatment may have beneficial effects on mood and sleep.

Isotretinoin and adverse neuropsychiatric outcomes: retrospective cohort study using routine data*

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Linked Comment: J. Ravenscroft and L. Eichenfield. *Br J Dermatol* 2022; **187**:8–9.

Abstract

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Conflicts of interest

S.L. is an employee of TriNetX LLC; no financial relationships with any other organizations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work. The other authors declare they have no conflicts of interest.

Data availability

Data were provided by TriNetX (<http://www.trinetx.com>), a federated data network. Access to TriNetX's de-identified patient data is available for the purpose of healthcare research with an approved user licence.

*Plain language summary available online

DOI 10.1111/bjd.21049

Background Severe neuropsychiatric outcomes have been reported in individuals exposed to isotretinoin, but the evidence is inconclusive and complicated by several methodological limitations.

Objectives To establish and quantify the association between isotretinoin use for acne and 1-year incident neuropsychiatric adverse outcomes.

Methods A propensity score-matched cohort study of electronic medical records between the years 2013 and 2019 with patients followed up for 1 year after their index dispensed prescription was conducted. The database included over 12 million patients aged 12–27 years. We analysed data for individuals with acne in this age range with a dispensed prescription for isotretinoin or a control prescription. Outcomes included diagnoses of any incident sleep or mental health disorder, or nonfatal self-harm within 1 year of the index prescription.

Results We included 30 866 patients prescribed isotretinoin for their acne, 44 748 prescribed oral antibiotics, 108 367 prescribed topical anti-acne agents and 78 666 patients with acne but without an anti-acne prescription. After propensity score matching for baseline confounders, the odds ratio (OR) for any incident neuropsychiatric outcomes in patients with acne exposed to isotretinoin was 0.80 [95% confidence interval (CI) 0.74–0.87] compared with those on oral antibiotics; 0.94 (95% CI 0.87–1.02) compared with those using topical anti-acne medicines; and 1.06 (95% CI 0.97–1.16) compared with those without a prescription for anti-acne medicines. Patients exposed to isotretinoin experienced significantly more incident physical symptoms than patients in any of the three comparison cohorts.

Conclusions Isotretinoin was not independently associated with excess adverse neuropsychiatric outcomes at the population level. When monitoring potential adverse outcomes during isotretinoin treatment, clinicians should also consider the high mental health burden associated with treatment-resistant acne and the potential contribution of physical side-effects of prescribed medication on mental health.

Acne on Isotretinoin in YP – risk of suicide

Case reports and small case series

- Reports depression and suicide death (eg Bachman 2007, Shaffer 2010, Sundström et al 2010)

Larger cohorts have not shown link including:

- 75,708 Isotretinoin cw oral antibiotics ($n = 75,708$). Global data. Risk of 9 psychiatric outcomes.
 - Isotretinoin confers lower risk of 6 psychiatric comorbidities. Comparable risk of suicidal attempts
 - Kridd et al JAAD 2022
- 7,535 patients with acne treated isotretinoin Canada & UK
 - Jick SS, et al Isotretinoin use and risk of depression, psychotic symptoms, suicide, and attempted suicide. *Arch Dermatol* 2000
- 100 patients with acne treated isotretinoin in Czech republic
 - Nevoralová Z et al Mood changes, depression and suicide risk during isotretinoin treatment: A prospective study. *Int J Dermatol* 2013
- 129 patients improved symptoms on PROM depression scores Isotretinoin in conscripts in Finland
 - Rehn et al JEADV 2009
- Small recent study showed no increase in impulsivity on Isotretinoin
 - (17 patients age 18-30) (Ogut et al 2024)

Droitcourt C et al.. Risk of suicide attempt associated with isotretinoin: a nationwide cohort and nested case-time-control study. *Int J Epidemiol* 2019

Table 1 Characteristics of patients with suicide attempt (SA) or completed suicide under isotretinoin and characteristics of courses of isotretinoin

	Patients with suicide attempt (n = 184)	Patients with completed suicide (n = 17)
Intentional self-harm by other and unspecified firearm discharge, n (%)	0 (0)	1 (5.9)
Intentional self-harm by sharp or blunt object, n (%)	18 (9.9)	1 (5.9)
Intentional self-harm by jumping from a high place, n (%)	1 (0.5)	1 (5.9)
Others, n (%)	20 (11)	5 (29.4)
Incidence rate (per 100 000 person-years), per calendar year		
Year 2010	147.9	12.7
Year 2011	90.7	5.7
Year 2012	125.5	17.1
Year 2013	102.5	8.3
Year 2014	95.6	8.0

IQR, interquartile range; N, number of patients with suicide attempt under isotretinoin; SA, suicide attempt; SD, standard deviation.

†Anxiolytic treatment alone identified using the ATC codes: N05BA, N05BB and N05BX.

‡History of hospitalized suicide attempt in the 12 months before the start of the course of isotretinoin identified using the ICD-10 diagnostic codes X60.x–X69.x, X70.x–X79.x and X80.x–X84.x (codes defined in Table S1), and/or history of psychiatric illness defined by long-term psychiatric illness status (long-term chronic disease giving entitlement to 100% health insurance coverage) and/or hospitalization in medical or surgical unit for psychiatric disorder identified using the ICD-10 diagnostic codes F05.x–F09.x, F10.x–F19.x, F20–F29, F30–F39, F40–F49, F50–F59, F60–F69, F80–F89, F90–F98 and F99 (codes defined in Table S2) and/or hospitalization in a psychiatric unit and/or psychotropic treatment, identified using the anatomical, therapeutic and chemical classification (ATC) codes: ATC: N05AX, N06XX, N07BB and N07CC.

§Total percentage can be >100 because cases could have two or more mode of suicide attempt for the same hospitalization.

Summary

Reportedly high incidence of suicidal attempts in patients with severe acne may be **representative of the combined baseline risk in this age** and the higher prevalence of acne towards late adolescence

Isotretinoin not shown to be risk factor for suicide

More likely to be protective

- No association with timing
- No statistical relationship with dose
- **Lower incidence of suicide cw controls**

The occurrence of mental health symptoms in isotretinoin-treated adolescents

Keith Miller MD¹  | Alastair McKean MD¹ | Jennifer Hand MD² |
Sandra Rackley MD, MAEdHD¹ | Jonathan G. Leung PharmD, RPh^{1,3}  |
Allison LeMahieu MS⁴ | Jennifer Geske MS⁴ | J. Michael Bostwick MD, MFA¹

- Retrospective cohort
- 606 patients 12-18 prescribed Isotretinoin (2008-2017)
- **177 psychiatric diagnosis prior to Isotretinoin (29.2%)**
- 98 new diagnosis while on Isotretinoin (16.2%)
- Those with **prior diagnosis** did experience more psychiatric symptoms
 - largely mood disorder and mood swings
- Dose change more common if new symptoms and no psychosocial explanation for psychiatric symptoms

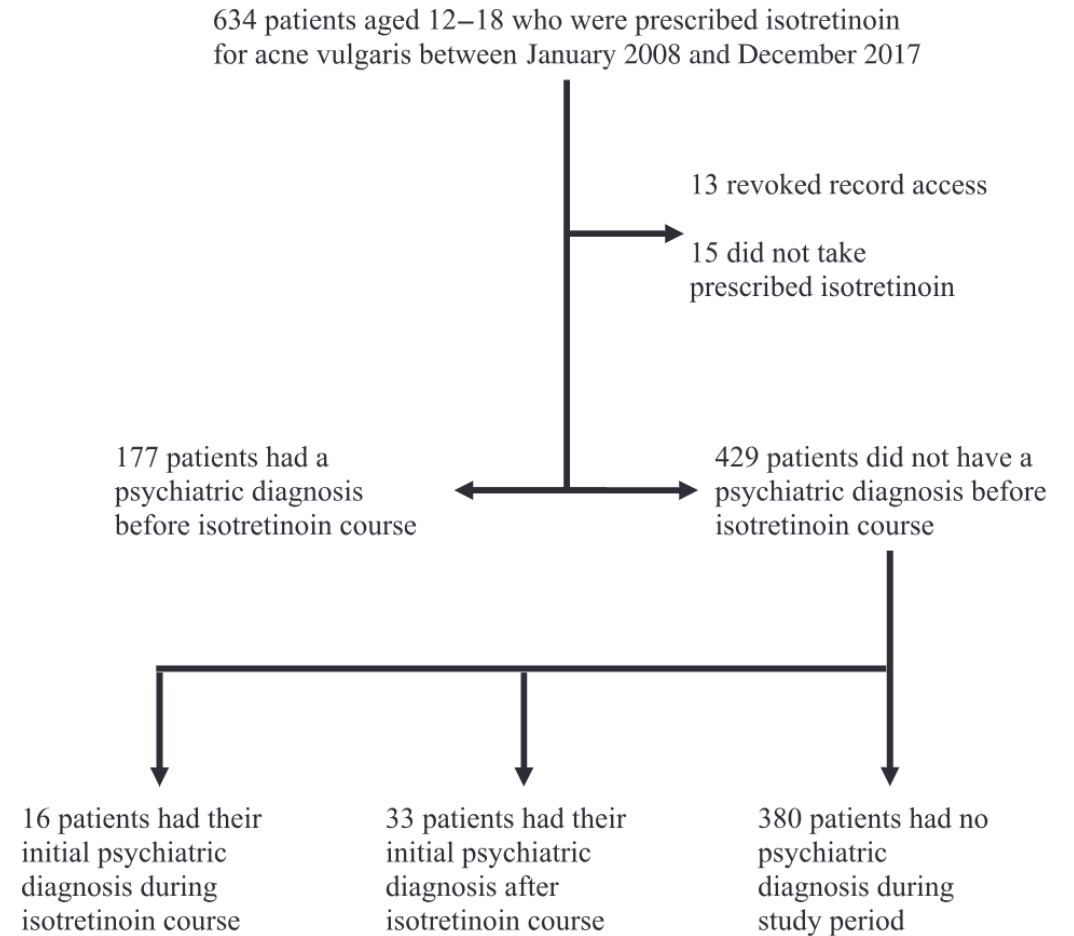


FIGURE 1 Sample of adolescent patients prescribed isotretinoin for acne vulgaris and timing of psychiatric diagnoses.

Tan et al 2024

Recent large meta-analysis

- 25 studies 1625891 patients on Isotretinoin Age 16 - 38 years
- 1-year pooled absolute risk 2 and 8 studies of
 - completed suicide, suicide attempt, suicide ideation, and self-harm less than 0.5%
 - depression was 3.83% (95% CI, 2.45-5.93; $I^2 = 77\%$)
- 11 studies. Isotretinoin users less likely than nonusers to attempt suicide
 - 2 years (RR, 0.92; 95% CI, 0.84-1.00; $I^2 = 0\%$)
 - 3 years (RR, 0.86; 95% CI, 0.77-0.95; $I^2 = 0\%$)
 - 4 years (RR, 0.85; 95% CI, 0.72-1.00; $I^2 = 23\%$) following treatment.
- Isotretinoin was not associated with the risk of all psychiatric disorders (RR, 1.08; 95% CI, 0.99-1.19; $I^2 = 0\%$).
- Population level - Isotretinoin
 - Lower risk of suicide
 - Lower risk of mood disorders

Research

JAMA Dermatology | Original Investigation

Risk of Suicide and Psychiatric Disorders Among Isotretinoin Users A Meta-Analysis

Nicole Kye Wen Tan; Adelina Tang; Neil Chen Yi Lun MacAlevey; Benjamin Kye Jyn Tan, MBBS(Hons);
Hazel H. Ong, MD

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)	More common among non-isotretinoin users	More common among isotretinoin users
Suicide attempt during treatment				

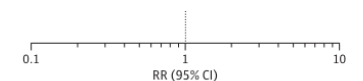
Key Points

Question Is isotretinoin use associated with the risk of suicide and psychiatric disorders?

Findings In this meta-analysis of 25 studies including 1 625 891 participants, the 1-year absolute risk of completed suicide, suicide attempt, suicide ideation, and self-harm among isotretinoin users was less than 0.5% each, while that of depression was 3.83%. Isotretinoin was not associated with the relative risk of all psychiatric disorders, and isotretinoin users were less likely than nonusers to attempt suicide at 2 to 4 years following treatment.

Meaning These findings indicate that there is no epidemiological evidence to suggest an increased relative risk of suicide or psychiatric conditions among isotretinoin users at a population level.

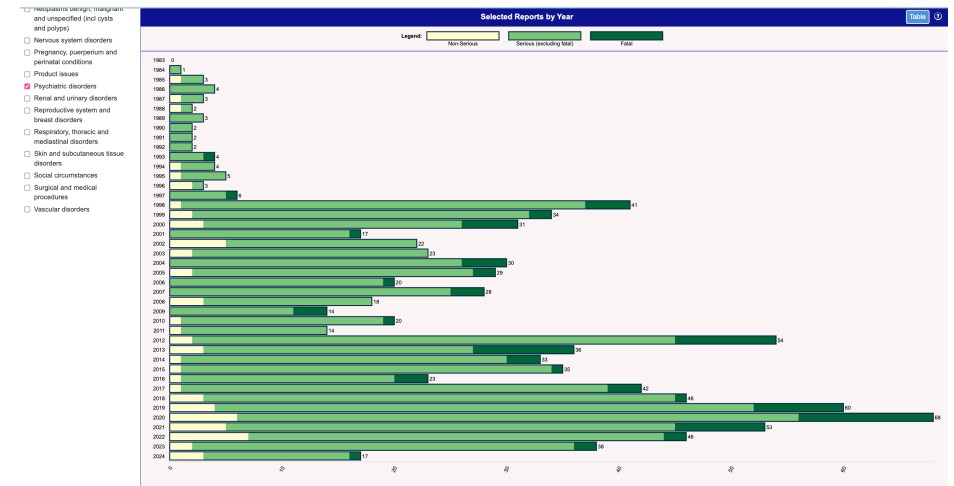
Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $I^2 = .88$
Test for subgroup differences: $\chi^2 = 4.74$, $P = .69$



Diamonds represent the estimated pooled relative risk ratio (RR) for each meta-analysis; gray box sizes, the relative weight apportioned to studies in each meta-analysis.

1983- 2024 – where are we now?

- Robust data that Isotretinoin does NOT confer risk at populations level
 - Evidence in fact is that it reduces risk
- Acne confers significant mental health risk
- Young people do complete suicides on Isotretinoin but this is rare
- Individual ‘idiosyncratic’ responses remain possible ?mechanism
- Remains contentious
- Can we (ever) prove or completely exclude causality?



Depression—a side effect of 13-*cis*-retinoic acid therapy

To the Editor:

Reported side effects of 13-*cis*-retinoic acid (isotretinoin) have included cheilitis, xerosis, skin fragility, bone aching, headache, stomach upset, alopecia, and corneal abnormalities.¹ We now wish to report another side effect recently observed by us—depression.

Six of 110 patients (5.5%) with acne or keratinizing disorders treated with 1.0 to 2.0 mg/kg body weight/day experienced depressive symptoms while on the drug. The depression was present in five patients with acne and in a single patient with palmar-plantar keratoderma associated with hypohidrotic ectodermal dysplasia. Four patients were women and two were

1/7

REVIEW ARTICLE

JAMA Dermatology | Original Investigation Risk of Suicide and Psychiatric Disorders Among Isotretinoin Users A Meta-Analysis

Nicole Kye Wen Tan, Adeline Tang, Neil Chen Yi Lun MacAuley, Benjamin Kye Jyn Tan, MBBS(Hons), Hazel H. Oon, MD

IMPORTANCE Isotretinoin is hypothesized to contribute to the development of psychiatric disorders, but the epidemiological association and risk factors associated with psychiatric disorders among isotretinoin users remain unclear.

OBJECTIVE To clarify the absolute and relative risk and risk factors associated with suicide and psychiatric disorders among isotretinoin users.

DATA SOURCES PubMed, Embase, Web of Science, and Scopus were searched from inception until January 24, 2023.

STUDY SELECTION Randomized trials and observational studies were selected if they reported the absolute risk, relative risk, and risk factors for suicide and psychiatric disorders among isotretinoin users.

DATA EXTRACTION AND SYNTHESIS Relevant data were extracted and evaluated at the study level using the Newcastle-Ottawa Scale. Data were pooled using inverse variance-weighted meta-analyses. Heterogeneity was measured using the I² statistic.

RESULTS A total of 25 studies including 1 625 891 participants were included in the meta-analysis. Among the included studies, participants' ages ranged from 16 to 38 years, and distribution by sex ranged from 0% to 100%.

CONCLUSIONS AND RELEVANCE The findings suggest that at a population level, users do not have an increased risk of suicide or psychiatric condition.

Suicide and Suicidality in Children and Adolescents with Skin Disorders: A Systematic Review

Richard BARLOW¹, Girija PAPPAYAZHI², Sarah HOGAN³, Dougal GRINDLAY⁴, Dr PASUNURU⁵, Ruth TAYLOR³, Anthony BEWLEY³ and Padma MOHANDAS³
¹University Hospital Coventry and Warwickshire, Coventry, ²Cardiff and Vale University Health Board, Cardiff, ³Centre of Evidence Based Medicine, Nottingham, and ⁴Aneurin Bevan University Health Board, Cardiff

Suicide in young children is rare; the incidence increases towards the end of adolescence. Skin disorders confer a high prevalence of psychiatric and psychological comorbidities. However, published research on suicidal behaviour in adolescents and children with skin disorders is sparse. The aim of this study was to identify the prevalence of suicidal behaviour in children and adolescents under 18 years of age with chronic skin disorders and associated contributing risk factors. MEDLINE, PsycINFO, EMBASE, CINAHL and Cochrane databases were searched from inception to October 2020 for suicide or suicide attempts in patients under 18 years old with chronic skin disorders. The study protocol was logged on PROSPERO (CRD42020083528). Returned texts were reviewed

SIGNIFICANCE

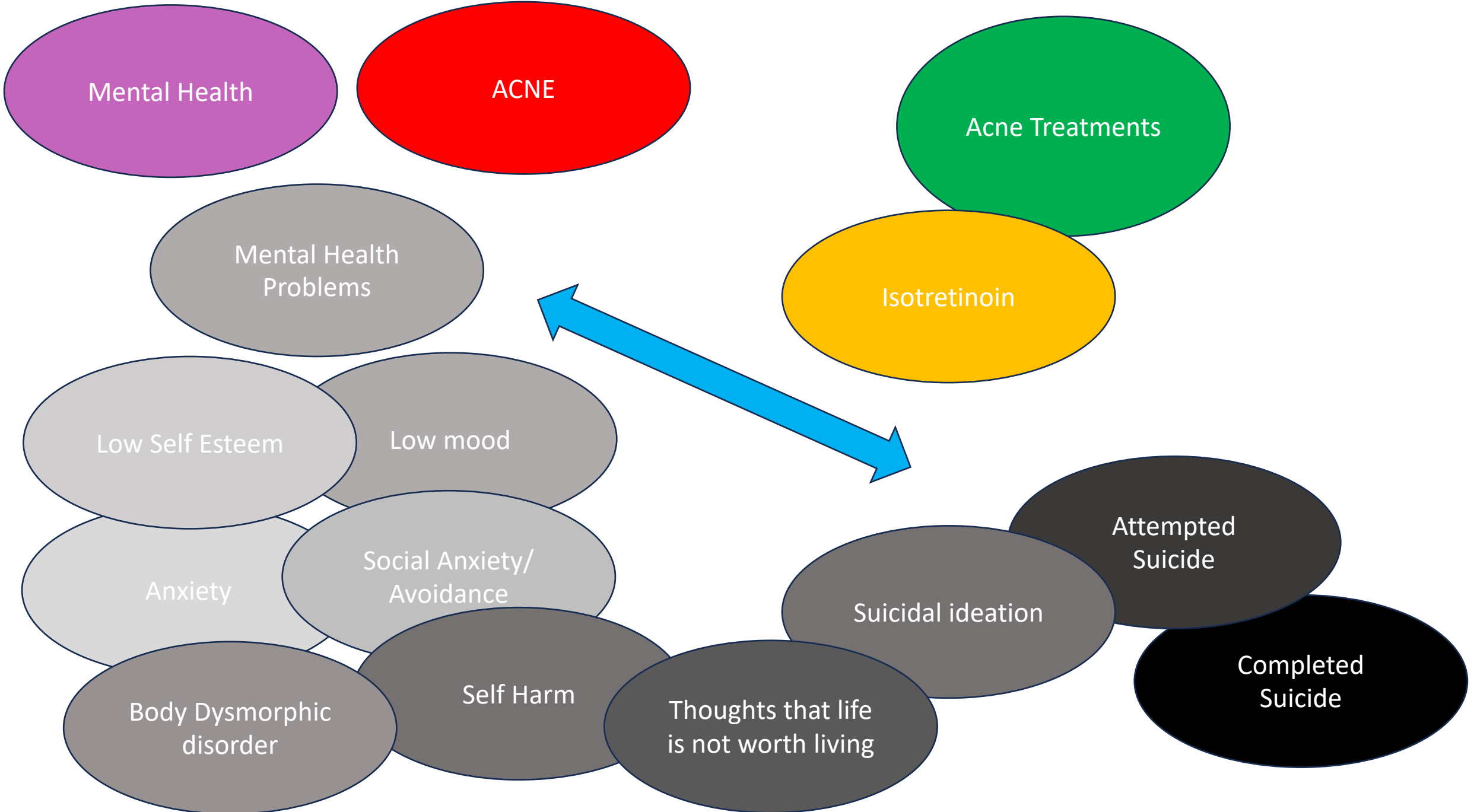
This study examined the prevalence of suicidal behaviour in children and adolescents with skin disorders. The findings show that the prevalence of suicidal behaviour in children and adolescents with skin disorders is low, but it is higher in those with chronic skin disorders. The study also identified risk factors for suicidal behaviour in children and adolescents with skin disorders, including family history of mental health problems, comorbid psychiatric disorders, and access to suicidal agents.



Epidemiology | Open Access | CC BY

Isotretinoin and adverse neuropsychiatric outcomes: retrospective cohort study using routine data

Tapio Paljarvi, Tess McPherson, Sierra Luciano, Kimmo Herttua, Seena Fazel



Conclusion Evidence & Risk



- Medicine is about assessing risk and reducing risk
- Population level data can inform but individuals remain individuals

Balance:

- Risk of not treating acne
- Risk of treatments
 - All treatments have some risk and longer-term risks remain largely unknown (oral antibiotics have risks!)
- Risk of over treating acne
- Risk of over medicalizing / society tolerance of skin problems

Conclusion

Effective treatment



- Acne has impact on mental health – short and longer term (esp scarring)
- Isotretinoin is effective to treat Acne
- Benefits outweigh risks in patients where Isotretinin is indicated

Conclusion

Support mental health

- Young people are vulnerable
- Young people with acne are even more vulnerable
- Patients with acne need support for mental health
- Whatever treatment they are on
- Guidance from BSPAD / BAD



Guidelines on the management of mental health in young people living with skin conditions¹ BSPAD 2023

Summary of recommendations

R1	Ask all CYP living with a skin condition about the emotional impact of their skin condition and about their general mental health - How is your skin (condition) making you feel?
R2	Be alert to non-verbal signs (e.g., low affect, concerns about being examined, signs of self-harm)
R3	Seek information from parents/carers about the emotional wellbeing and impact of skin disease on CYP; involve them in decisions and support where possible
R4	Document impact on QoL in all CYP with a skin condition; consider using an appropriate PROM (e.g., CDLQI, TQoL, PedsQL)
R5	Document current and previous mental health needs, including GP, school, CAMHS etc., include relevant info. from referral letters and communications
R6	Offer an assessment for depression and anxiety in CYP where psychological concerns arise; consider using an appropriate PROM
R7	Be aware that coexisting neurodiversity, neurodevelopmental disorders or mental illness can affect the presentation and lived experience of skin conditions
R8	Offer CYP with skin conditions advice on support when there are psychological concerns
R9	Refer CYP with psychocutaneous conditions or where psychodermatology issues are affecting disease treatment/progress to a regional, comprehensive psychodermatology service or refer for discussion at a psychodermatology regional or national MDT
R10	Communicate with relevant health, education and social services when psychological concerns arise – include GP in all correspondence
R11	Ensure that training opportunities are available for all members of staff on the recognition and support of mental health conditions and neurodevelopmental conditions in this population

CYP, children and young people

1. McPherson T, et al. Br J Dermatol. 2023;189(4):459-66. 2. Brouwers MC, et al. Can Med Assoc J. 2010;182(18):E839-42.

Thanks and Questions??
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Resources:

British association of dermatology

<https://www.skinhealthinfo.org.uk/support-resources/acne-support/>

www.bspad.co.uk

www.healthtalk.org

Patient experiences resource: Rigorous and systematic research methods for patient interviews

Shown to make patients feel less alone with condition and find solutions to problems

ACNE, ALOPECIA, ECZEMA & PSORIASIS available since 2017

Book – Skin conditions in Young People.

A practical guide on how to be comfortable in your skin. (published OUP 2021)

- Information on 'Normal' Skin, Many skin conditions including acne and managing impact of skin conditions





