Supplement to: The risk for depressive mood changes emerging with isotretinoin treatment is significantly increased by prior mental health history, but not dose-dependent.

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Materials & Methods

Ethics Statement and Governance approval.

The data presented here were compiled in accordance with local R&D research guidelines and subject to prior ethics and patient – data handling review and approval (Caldicott approval ref-nr IGTCAL3351).

Overall study design

This is an observational study combining prospective and retrospective elements: the primary study endpoint, defined as "clinician - identified treatment – limiting depressive mood changes emergent with isotretinoin treatment dispensed for acne" is captured prospectively. Secondary endpoints were also recorded prospectively: (i) "clinician – recorded prior personal or family history of mental health (MH)", (ii) daily dose at time-of-discontinuation, and (iii) time-to-discontinuation in affected patients. Study format, statistical analyses, database interrogation were performed retrospectively.

Definition of observational window

The observational window was set to commence from 1st January 2005 as to maximise data availability of electronic data retrieval held by NHS Tayside pharmacy. The end of the observation window was set to 31st July 2019, this was dictated by availability of data with completion of treatment course within this time.

Cohort identification

In NHS Tayside, prescription of isotretinoin is secondary-care restricted and all scripts for the entire catchment population are processed through a central pharmacy. This list was procured initially, representing all isotretinoin treatment courses dispensed between 1 Jan 2005 and 28 Feb 2018 (n = 3497). Next, this dataset was linked with a list of community health index (CHI) numbers for all patients with a diagnosis of acne contained in Dermabase (entry limits 2000 – 2019) using Business Objects software (n = 8756), yielding n = 3151 isotretinoin patients for acne, and n = 158 for non-acne patients, respectively, n = 188 having received isotretinoin courses outwith Dermatology. The latter subgroup was disregarded for the present analysis. Details of the resultant treatment parameters are shown in table 1.

Clinical data extraction, initial cohort construction, and prior mental-health related history

All isotretinoin treatment courses in NHS Tayside are initiated after review through secondary care dermatology, which triggers a communication to the patient's GP which is electronically captured on the Dermabase system. We used Business Objects software using the following search strings to retrieve all datasets containing relevant clinical information: the term 'acne' in the letter body as well as 'Roaccutane' or 'isotretinoin' in letter body in all datasets generated between 1/1/2005 – 31/07/2019. This yielded an initial dataset of n = 8756 GP correspondence letters. Pre-treatment mental history is captured by a mandatory baseline questionnaire including the question: "Any personal or family history of psychiatric illness (particular depression)." The questionnaire does not attempt to confirm a specific psychiatric diagnosis. Completeness of these data is shown below (section "Completeness of data and risk of bias"). In addition, the presence and absence of any prior mental-health history was identified using the following electronic patient record search string array: 'low mood', 'suicid*'(capturing: "suicide", "suicidal"), 'depres*'(depression, depressed), 'anti-depres*', the list of most commonly prescribed medication ('sertraline', 'citalopram', 'mirtazapine', 'venlafaxine') and 'anx*'(anxiety, anxious), as well as 'mental', 'bipolar', 'schizo*'.

Cohort refinement and identification of clinical endpoints

The initial data-set was refined by electronic verification of acne-related diagnostic terms as being active at the time of treatment (as opposed to, for example, having been relevant at a previous encounter with dermatology). Next, the clinical dataset was linked to the pharmacy dispensing database (see above) and the resultant list of GP communication letters were loaded into Excel spreadsheets. The main endpoint, isotretinoin - associated mood changes, was identified by identifying texts containing a number of permutated search strings as follows: 'low mood', 'suicid*'(capturing: "suicide", "suicidal"), 'depres*'(depression, depressed), 'anti-depres*', the list of most commonly prescribed medication ('sertraline', 'citalopram', 'mirtazapine', 'venlafaxine') and 'anx*'(anxiety, anxious). These letters were then examined manually to determine if treatment was halted due to mood related issues (see Letter). Search strings to

capture any mental health history in the dataset were expanded to contain: ‘mental’, ‘bipolar’, ‘schizo*’.

Extraction of additional clinical information and dosing quantities

The availability of CHI numbers allowed identification of gender (coded in the penultimate numeral). Age at time of treatment was extracted by matching patients’ date of birth to initial dosing date. Dose quantities were available as sum of isotretinoin per treatment course for all patients, while daily doses could only be calculated for female patients through the availability of dispensing events and the legally restricted dispensing interval of 30 days per dispensed item. The resultant calculated overall average daily dose was further corrected by the standard departmental policy of treatment initiation using 50% of the intended steady-state dose of 1 mg / kg body weight. (see table S1).

Treatment emergent dose limiting depressive mood changes

To determine the incidence of isotretinoin associated mood changes, we applied a string of search terms (see below) to the database of all communications sent from specialist care, where isotretinoin treatment is being conducted, to patients’ GPs. The underlying assumption is that an adverse event of sufficient severity to warrant discontinuation of treatment as judged by the clinician supervising treatment is unlikely not to be communicated in the resultant GP communication. By contrast, treatment-emergent AE’s assessed to be less-than-severe by patient and / or clinician will be subject to under-reporting, thereby incurring a reporting bias of unknown magnitude in the data record. For that reason, we did not analyze in detail the additional subgroup of patients identified with non – treatment limiting mood changes (n = 25). Search strings applied were as follows: depress*, agitat*, melanchol*, anxious, anxiety*, agress*, mood, sad, irritab*, “feeling low”. Technically, the identified treatment-emergent mood changes are therefore clinician-reported. However, in each case this represents clinician assessment of patient self-reporting. All resultant primary data are listed in Supporting Dataset.

Completeness of data and risk of bias

Primary endpoint: Electronically captured GP communication available for database search was available for 100% of patients. Under reporting of reason for treatment discontinuation is a theoretical systematic risk. Failure to capture relevant information by non-comprehensive search strings (see above) is another risk. These two factors leave open a possibility that the true incidence rate is higher than observed. However, it is unlikely that missing data would substantively affect observed outcomes. Secondary endpoints: (i) dosing information: pharmacy-recorded drug dispensing data was available for 100% of patients; (ii) information of prior mental history: previous internal data audit confirmed that completion rate of the departmental process of recording mental health history is 94 %.

Calculation of statistical power

Using the overall sample size as background population, and assuming a prevalence of 10% of depressive illness a priori, a sample size of n = 3150 allows for detection of an incidence of treatment-emergent depressive mood changes in at least 12% of cases with a power of 95% (alpha = 0.05).

Extended Results

Quantitative analysis of isotretinoin dosing in acne.

The available pharmacy data included total isotretinoin amounts dispensed per treatment course (table 1), as well as the number of dispensing episodes, but not the daily dose regimens for all patients. However, for female patients dispensing is legally restricted to thirty days, allowing indirect calculation of resultant daily doses. Thus, about 95% of female patients received doses between 50 – 100 mg per day (Fig. S3) and average treatment duration was approximately five months (158 ± 113 days, Fig. S4). Dose levels did not show any association with patient age (Fig. S5).

Table S1.

Clinical characteristics of acne patients exhibiting treatment – limiting depressive mood changes associated with isotretinoin treatment.[1]

	Treatment limiting depressive mood changes	
	Yes	No
N	30	3121
Age (mean ± s.d.)	22.8 ± 7.9	21.5 ± 8.2
Gender (% female)	50.0	50.0
Total dose (gram)	4.9 ± 2.8	8.1 ± 5.4*
Daily dose at treatment end (mg)[2]	46.8 ± 20.5	52.9 ± 28.8
History of Mental illness n (%)	10 (33.3)	207 (6.6)***

[1] For patient – specific details, see Table S2.

[2] Calculated only for female patients due to data availability (see Methods).

* p = 0.002 (two-tailed T-test, unequal variance).

***p < 0.000 (Chi-square)

Table S2.
The frequency of mental health history by gender in acne patients.

	Female (n = 1561)		**Male (n = 1560)**	
PMH[1]	146 (9.3 %)		71 (4.5 %)***	
	Treatment-limiting depressive mood changes			
	Yes	No	Yes	No
no PMH	8 (53.3 %)	1422 (91.1%)	12 (80 %)	1492 (95.6 %)
PMH	7 (46.7 %)	139 (8.9 %)	3 (20 %)	68 (4.4 %)
Relative risk[2]	8.9 [3.2 – 25]		5.4 [1.5 – 19]	

[1]Past medical history of depressive illness prior to treatment (see Methods for details).

[2] Risk ratio of treatment-limiting depressive mood changes occurring in patients with PMH [95% C.I.].

*** $p < 0.0001$, male vs female (Chi-square).

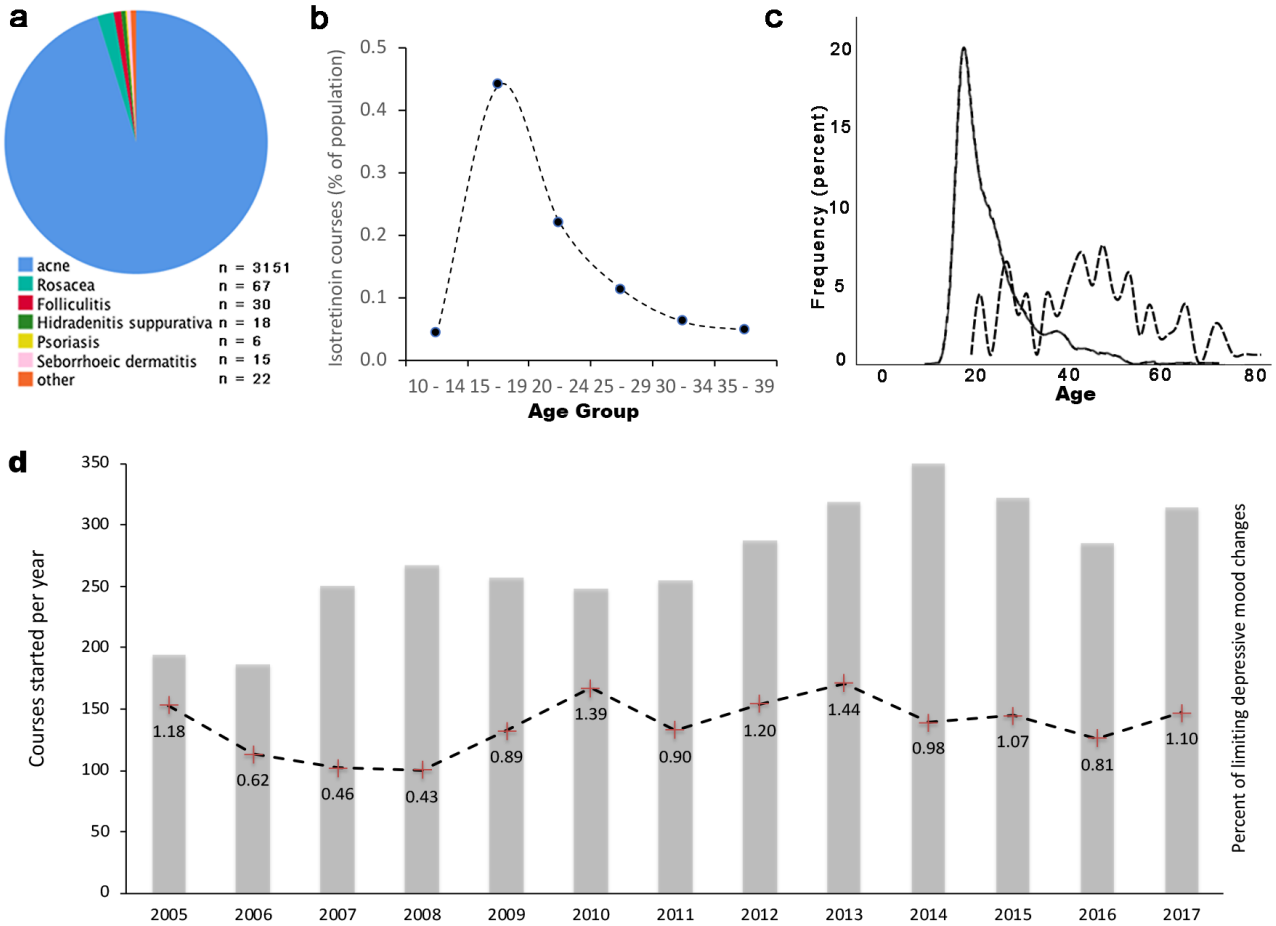
Table S3.
The frequency of isotretinoin courses initiated for acne per population in Tayside, Scotland

Age group[1]	Nr of courses	population	male	female	courses / pop[2]
10 - 14	115	20,976	10,733	10,243	0.04
15 - 19	1314	22,977	11,736	11,241	0.44
20 - 24	792	28,005	14,120	13,885	0.22
25 - 29	416	28,463	14,496	13,967	0.11
30 - 34	203	25,726	12,674	13,052	0.06
35 - 39	148	23,723	11,621	12,102	0.05

[1] Data shown are population estimates supplied by IDS Scotland for the index year 2017.

[2] Data shown are the percentage of annual incidence rates of treatment, derived by dividing the observed total number of courses started by the number of calendar years in the observational window (n = 13) and then by the population in each age group.

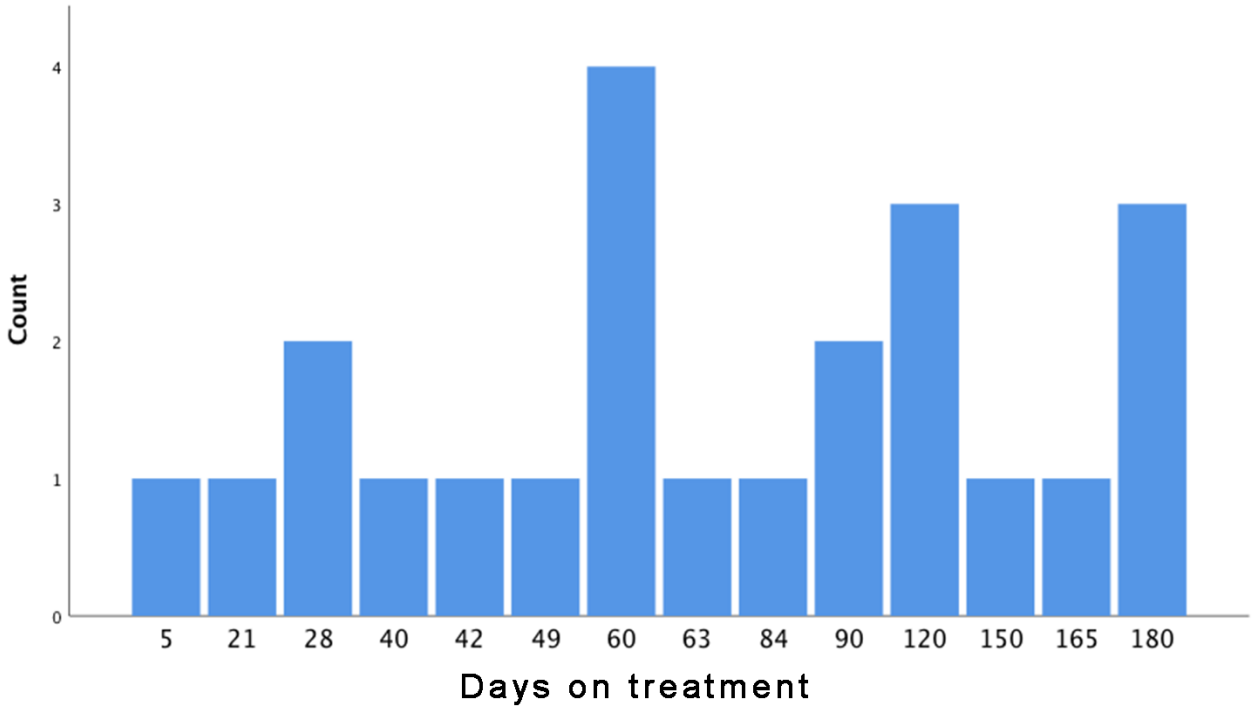
Figure S1



Isotretinoin dispensed in NHS Tayside 2008–2018. A. Distribution of indications, “Other”: sebaceous hyperplasia(n = 4), plane warts, Darier’s disease(each n = 3), Granuloma annulare, Perioral dermatitis,(each n = 2), Perifolliculitis capitis, pruritus, perforating collagenoma, pityriasis rubra pilaris, dissecting cellulitis, ectopic sebaceous glands, atopic and actinic dermatitis(each n = 1). B. The prevalence of treatment-initiation for acne as percentage of the general population(details see Table S5). C. Histogram of age at treatment for acne (solid line) and non-acne (dashed line). D. Number of Isotretinoin courses started for acne per year. Dashed line

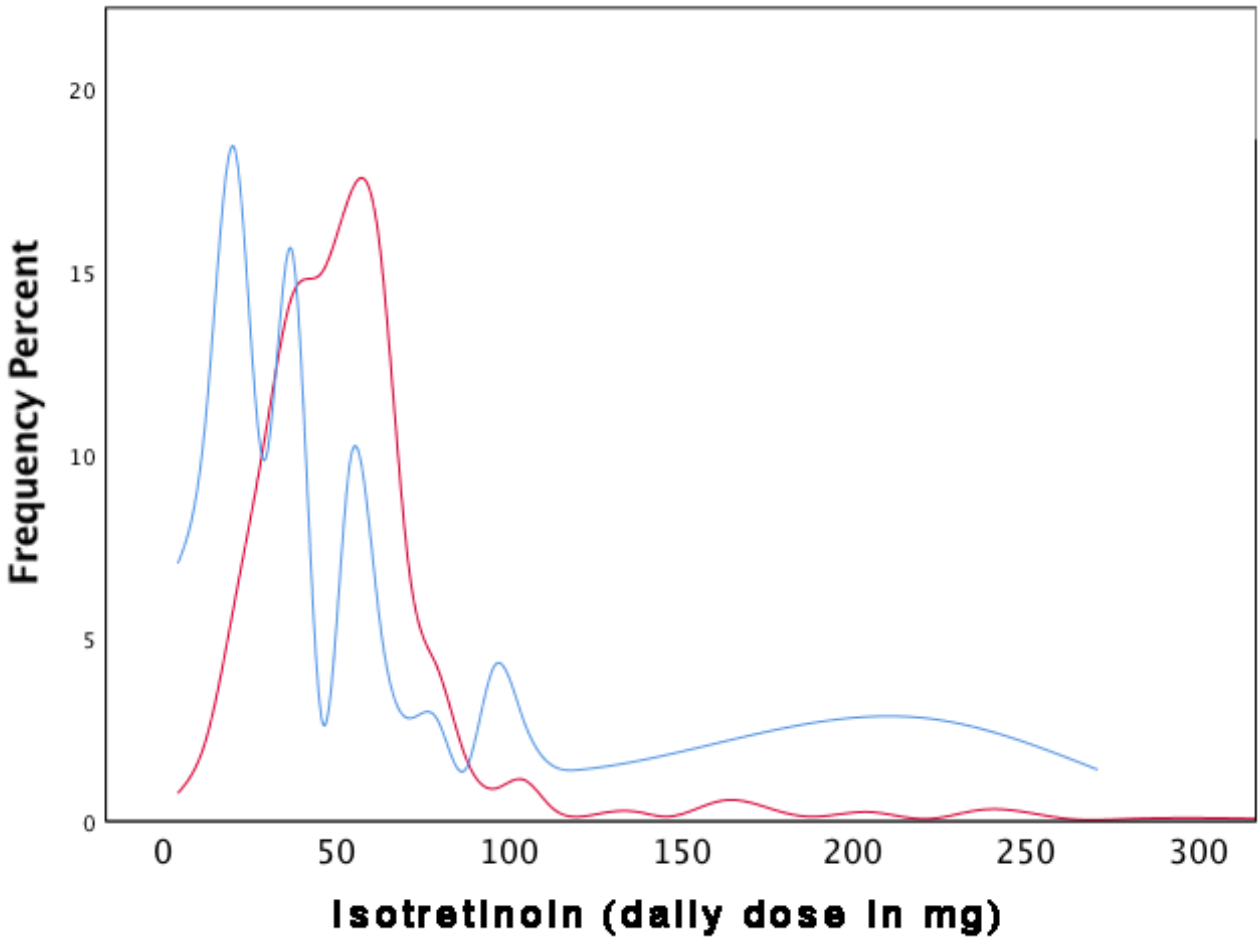
and numbers represent the percentage of treatment-limiting mood changes each year. There was a highly significant increase of yearly treatments ($r = 0.7$; $p < 0.0001$, correlation between year and treatment) but no association between the incidence of mood changes and treatment year ($r = 0.1$, $p > 0.05$).

Figure S2



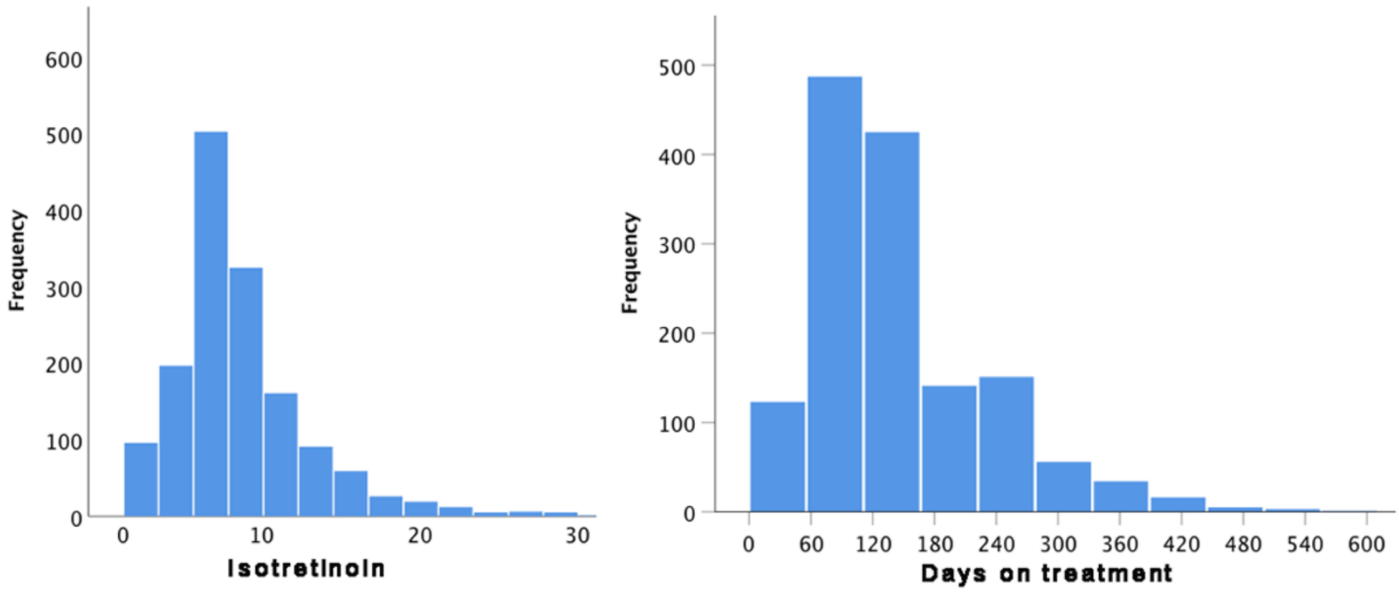
Distribution of treatment duration in acne – patients exhibiting dose-limiting depressive mood changes.

Figure S3



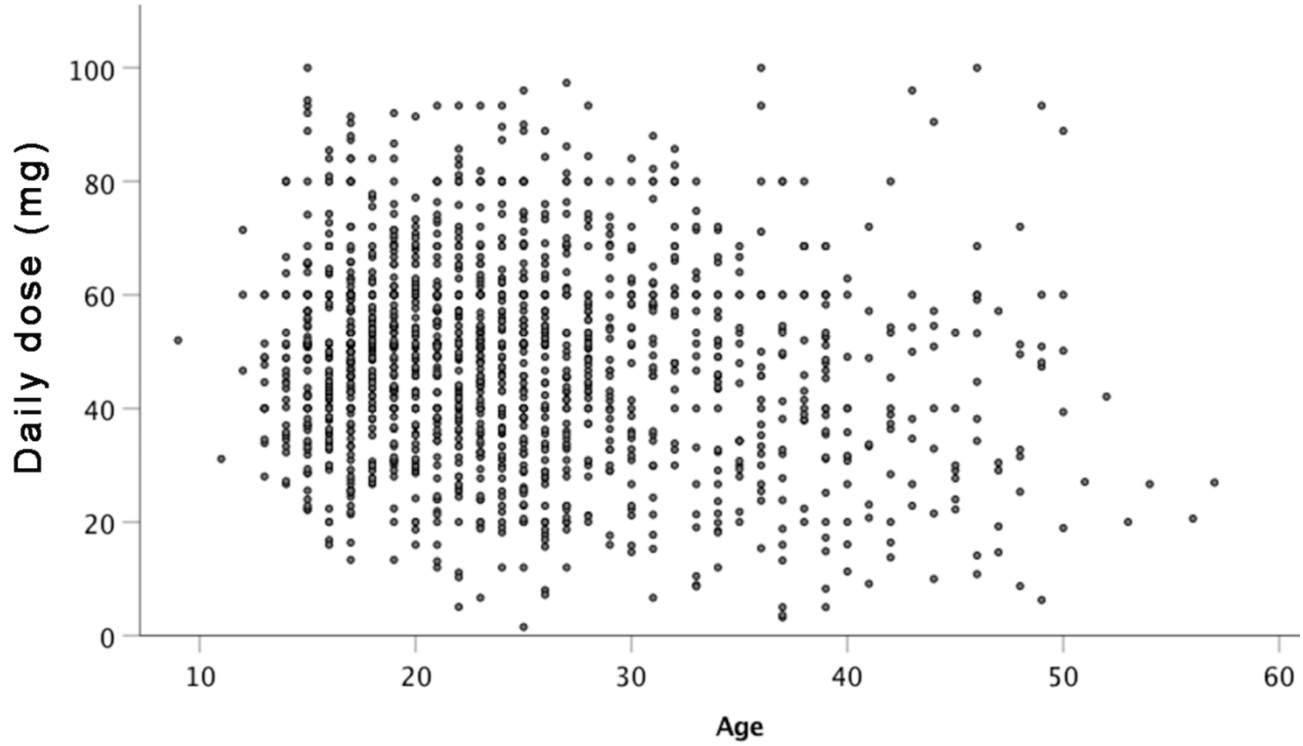
Daily dose at steady – state in female patients treated for acne (red, n = 1576) or non-acne conditions (blue, n = 71.). After exclusion of outliers (dose > 100 mg / day), the observed average dose for acne patients was significantly lower than that used for non-acne patients (37.5 ± 23.6 vs. 48.8 ± 17.6, $p < 0.0001$, 2-tailed T-test). Note the distinct peak heterogeneity in non-acne patients, indicative of patient subgroups receiving low-dose and/or pulse type treatments.

Figure S4. Cumulative total isotretinoin dose and treatment duration



Left: Histogram of total isotretinoin (in gram) dispensed to female patients, after excluding of outliers (Fig. S2, > 100 mg/d steady state dose), corresponding to 7.5 ± 4.8 gram (mean ± s.d.). Right: Histogram of treatment duration (days) in female patients dispensed total isotretinoin amounts (excluding outliers outwith two standard deviations of the mean, corresponding to 17.1 g). Note that the resolution along the time-axis is limited by the standard 30-day interval between subsequent medicine dispensed to each female patient.

Figure S5. Relationship between daily isotretinoin dose and age in female acne patients



Data shown represent steady-state dose in female acne patients receiving < 100 mg / day steady – state isotretinoin (n = 1515).

Supporting Dataset

Patient	Gender	Age	Days on treatment	Concurrent reason for stopping	Total Dose	Daily dose	Recorded wording
1	Fem	21	5		200	40	History of depression and self-harm; felt tearful and agitated after 5 days of Roaccutane; which she then stopped. was arguing with her partner with some physical and verbal abuse also. On cessation of drug feels back to herself.
2	Fem	16	21		900	30	Had been suffering from depression; depression has gotten worse since taking Isotretinoin for about 3 weeks. Isotretinoin was stopped and since then mood has improved but still suffers from depression. never had any suicidal thoughts but gives a history of intermittent thoughts of self-harm. she scored significantly for both depression and anxiety scores; also has a family history of depression.
3	Fem	22	28		4500	60	Developed quite a low mood after four weeks of Isotretinoin 60mg daily and skin was also flaring at this point so stopped Isotretinoin. mood then became even lower and she felt terrible and self-harmed for the first time, cutting her left arm. She is now feeling much better in herself, less depressed and has had no further thoughts of self-harm. She is not on any other medication currently and gives a history of anxiety but no previous depression.
4	Male	16	28		1200	60	Isotretinoin had to be withdrawn as he became depressed and there was a concern about suicidal ideas. his mood is now improving having come off the Isotretinoin.
5	Fem	34	40		1800	60	Sustained a rather severe episode of melancholy, mood swing and depression on Roaccutane after the dose increase from 30mg to 60mg; had run out of tablets and had been without any treatment for 3 weeks before; then was given the full dose straight away.
6	Male	22	42	muscle aches	7500	70	Had stopped the Isotretinoin following the increased dose to 70mg daily due to experiencing muscle aches and pains and low mood. mood is now back to normal and he noticed a difference within a week of stopping.
7	Fem	24	49		4200	70	After 7 weeks of 70 mg Roaccutane daily stopped treatment as she developed attacks of anxiety and episodes of depression. had this previously and was on medication for this. stopped her Roaccutane about 2 ½ weeks ago.

8	Fem	20	60		3000	70	Since commencing Isotretinoin has had increasing irrational anxieties, with worries about the death of a friend or relatives, feelings that people may be staring at her in public places, general background anxiety and some early morning wakening. describes no depressive features as such and has had no suicidal ideation. has not had medication for the last three days. She is already describing a reduction in symptomology.
9	Male	22	60		7200	20	Has been on 20 mg of Roaccutane for 7 weeks. noticed a change in his moods and [being] dead tired. Also sometimes was depressed. Subsequently he complained of sharp chest pain lasting a couple of seconds on and off. He wants to know if there are any other options available to him or whether Roaccutane was the only choice.
10	Male	24	60	elevated triglycerides	8100	30	On Roaccutane for his acne. I note that his triglycerides have risen. he was feeling depressed and wanted to discuss stopping Roaccutane anyway.
11	Fem	16	60		8100	30	Is currently on Roaccutane for her acne. has a previous history of bipolar psychosis and is being seen by psychiatry but has been attending somewhat sporadically, has also been taking her anti-psychotic medication, rather sporadically as well. had been tearful, but her mood was generally reasonable and she was definitely not suicidal. She therefore continued her dose of Roaccutane at 30mg daily, but [thereafter] had been feeling agitated and was expressing suicidal intent. She stopped her Roaccutane three days ago.
12	Fem	17	63		4500	60	Has now been taking Isotretinoin 30mg daily for 4 weeks and 60mg daily for 5 weeks for acne. During treatment there have been adverse effects of change in mood. has been suffering from panic attacks and low mood. in relation to this treatment has stopped.
13	Fem	16	84		3300	40	Has been on Roaccutane now for twelve weeks. Unfortunately, she has been troubled by irritability and episodes of low mood in the past week or so. This is a new phenomenon for her; In addition, she also reports waking with headache for the past two weeks, her headaches settle down during the day.
14	Male	15	90		4500	40	Had a further 2 weeks of Roaccutane at 40mg. He had not been feeling himself for a few weeks and it was noted that his mood had deteriorated significantly, become low and he had become generally irritable. This was attributed to his Roaccutane and things seem to have picked up since he stopped.
15	Fem	15	90		5400	60	Roaccutane has caused significant change in mood with spontaneous aggression and tearfulness – not overtly clinically depressed however.

16	Male	32	120	painful shoulders and elbows and flare of acne	3600	40	This gentleman, while he was taking his Isotretinoin 40mgs daily, had very low mood and painful shoulders and elbows. He also noted a flare of his facial acne which in fact had been clear initially; this activity is now settling. does not wish to continue the Isotretinoin
17	Male	17	120		12600	120	Stopped Isotretinoin in November last year because of reduced mood.
18	Fem	17	120		8400	60	Has now been taking Isotretinoin 40mg daily for 4 weeks and 60mg daily for 12 weeks for acne. she and her father indicated that she felt her mood has been very erratic and that she feels it is affecting her daily routine. her father noticed a large change in her behaviour and she agrees with this. There is no thought of self-harm or suicidal tendency
19	Male	15	150		6300	70	Came for review outwith the normal cycle because of a depressive mood change. quite possibly to do with his Isotretinoin treatment and I have therefore stopped the treatment.
20	Male	41	165	aches and pains'	9600	40	Is still experiencing aches and pains and general irritability which is dose related and he has continued to take his Isotretinoin at a lower dose of 40mgs. He would like to stop this now due to the side effects
21	Fem	39	180		960	5	Received 6 months of pulsed Isotretinoin taken 20mg once daily twice weekly. stopped due to increasing anxiety and low mood. put this down to University stresses as is currently approaching exam time and multiple assessments. However, the Pharmacist wondered about Isotretinoin exacerbating this and therefore stopped Isotretinoin
22	Fem	44	180		2400	10	had been managed with low dose Isotretinoin for the past 6 months or so. Unfortunately, 2 weeks ago she experienced an episode of low mood. history of depression for which she takes Venlafaxine and there were other external factors, mainly her father being unwell which may have contributed to her low mood. She sensibly stopped taking the Isotretinoin as a precaution and her mood does seem to be slowly improving. She never had any suicidal or self-harm ideation.
23	Male	15	180		2700	70	he has had some nose bleeds which are recurring regularly and also low mood. his mum reports that he does have quite a flat mood generally but there has been a deterioration whilst on the Roaccutane. Although he is managing his school work he is not interested in socialising at all outwith school.
24	Fem	23	30	dry flakey rash	2100	70	Unfortunately, she has had pronounced side-effects from isotretinoin and it has been discontinued. Possibly of more concern is the development of a low mood coinciding with starting Roaccutane, although she is feeling a bit better now off this drug.

25	Fem	19	90		3000	40	She did not complete the course of Roaccutane due to mood swings and depressed mood. This occurred once moving to 40mg Roaccutane
26	Male	18	110		4500	40	He stopped the Roaccutane 2 weeks ago secondary to unbearable side effects and feeling depressed.
27	Male	22	120		6000	50	Stopped taking the Roaccutane last week as he was aware of mood changes and anxiety symptom
28	Male	18	5		200	40	He had recently tried a course of Roaccutane at 40mg per day, unfortunately only a few days after starting treatment he began to feel unwell with a low mood and low energy levels
29	Male	16	60	developed colitis, dry eyes and a flare of eczema	3000	60	His mood has been progressively lowering in recent weeks and earlier this week he was tearful, refusing to go out of the house and in general feeling very low. He has been bullied on Facebook as a result of his skin condition and feels that his Roaccutane has made his appearance worse. He has been on isotretinoin 60mg once daily but this was stopped by his GP on Monday after discussion with ourselves.
30	Male	15	98	dry skin, sweating	2940	30	This young boy was reviewed back at clinic today. He was on low dose Roaccutane for 14 weeks and eventually stopped because he was experiencing low moods and severe dryness. During the course of treatment there have been adverse effects of dry bleeding lips, excessive sweating and lowering of mood. He has expressed feelings of a low mood in the past.

STROBE Statement

	Item No	Recommendation	Action
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	See Materials and Methods, Overall Study Design
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Not applicable for Research Letter
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	See Letter
Objectives	3	State specific objectives, including any prespecified hypotheses	See Methods, Overall Study Design
Methods			
Study design	4	Present key elements of study design early in the paper	See Methods, Overall Study Design
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	See Methods, Overall Study Design
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	See Methods, Overall Study Design
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed	Not applicable

		Case-control study—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	See Methods
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	See Methods
Bias	9	Describe any efforts to address potential sources of bias	See Methods
Study size	10	Explain how the study size was arrived at	See Methods, Calculation of Statistical Power
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Not applicable, main variable is qualitative
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Statically tests used are detailed in each respective table and figure legend
		(*b*) Describe any methods used to examine subgroups and interactions	See table S2
		(*c*) Explain how missing data were addressed	See Methods
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	Not applicable as the dataset was defined by completed treatment episodes
		(*e*) Describe any sensitivity analyses	Not applicable

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	See Methods, Cohort identification
		(b) Give reasons for non-participation at each stage	See Methods, Cohort identification
		(c) Consider use of a flow diagram	Not done
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	See Letter
		(b) Indicate number of participants with missing data for each variable of interest	Not applicable
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	See Methods, Definition of observation window
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	See Letter
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	N/A
		Cross-sectional study—Report numbers of outcome events or summary measures	N/A
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	See Letter
		(*b*) Report category boundaries when continuous variables were categorized	See Letter
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	See Letter
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	See Letter
Discussion			
Key results	18	Summarise key results with reference to study objectives	See Letter

Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	See Letter
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	See Letter
Generalisability	21	Discuss the generalisability (external validity) of the study results	See Letter
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	See Letter