Risk of suicide attempt associated with isotretinoin a nationwide cohort and nested case-time-control study

Catherine Droitcourt, Emmanuel Nowak, Caroline Rault, André Happe, Béranger Le Nautout, Sandrine Kerbrat, Frédéric Balusson, Florence Poizeau, David Travers, Jean-Marc Sapori, et al.

Risk of suicide attempt associated with isotretinoin: a nationwide cohort and nested case-time-control study

Catherine Droitcourt,[1,2,3,4†] Emmanuel Nowak,[2,5,6†] Caroline Rault,[1,2] Andre´ Happe,[1,2] Be´ranger Le Nautout,[1,2] Sandrine Kerbrat,[1,2] Fre´de´ric Balusson,[1,2] Florence Poizeau,[1,2,3] David Travers,[7] Jean-Marc Sapori,[8] Emmanuel Lagarde,[9] Gre´goire Rey,[10] Bernard Guillot,[11] Emmanuel Oger[1,2†] and Alain Dupuy[1,2,3*†]

[1]Univ Rennes, EA 7449 REPERES [Pharmacoepidemiology and Health Services Research], [2]PEPS Research Consortium (Pharmacoepidemiology for Health Product Safety), Rennes, France, [3]Department of Dermatology, CHU Rennes, Rennes, France, [4]INSERM, CIC 1414, Rennes, France, [5]University of Bretagne Loire, University of Brest, France, [6]INSERM CIC 1412, CHRU Brest, Brest, France, [7]Department of Psychiatry, CHU Rennes, Rennes, France, [8]Emergency Department, CHU Lyon, Lyon, France, [9]INSERM, ISPED, Bordeaux Population Health Research Center INSERM U219 – "Injury Epidemiology Transport Occupation" Team, Bordeaux Cedex, France, [10]CépiDc-INSERM, Le Kremlin-Bicêtre, France and [11]Department of Dermatology, CHU Montpellier, Montpellier, France

*Corresponding author. Department of Dermatology, Pontchaillou Hospital, 2 rue Henri le Guilloux 35000 Rennes, France. E-mail: alain.dupuy@chu-rennes.fr

[†]These authors contributed equally to this work.

Abstract

Background: Isotretinoin is the only effective treatment for severe acne. An isotretinoin-related suicide risk is still debated and under scrutiny by regulatory agencies. Our objectives were: to assess the risk of suicide attempt before, during and after isotretinoin treatment; to detect any potential triggering effect of isotretinoin initiation on suicide attempt.

Methods: We implemented a cohort and nested case-time-control study of subjects treated with oral isotretinoin (course or initiation) aged 10–50 years, using the Nationwide French Health Insurance data (2009–2016). The main outcome was hospital-ized suicide attempt. Standardized incidence ratios for hospitalized suicide attempts were calculated before, during and after isotretinoin treatment. The number of isotretinoin initiations was compared in risk and control periods of 2 months using a case-time-control analysis.

Results: In all, 443 814 patients (median age 20.0 years; interquartile range 17.0–27.0 years) were exposed to isotretinoin, amounting to 244 154 person-years, with a marked seasonality for treatment initiation. Compared with the French general

population, the occurrence of suicide attempts under isotretinoin treatment was markedly lower, with a standardized incidence ratio of 0.6 [95% confidence interval (CI) = 0.53–0.67]; the same applied, to a lesser extent, before and after isotretinoin treatment. In the case-time-control analysis, among cases of suicide attempt, 108 and 127 isotretinoin initiations were observed in the risk and control periods respectively (i.e. 0–2 months and 2–4 months before the date of suicide attempt). The comparison with the 1199 and 1253 initiations observed among matched controls in the same two periods yielded a case-time-control odds ratio of 0.89 (95% CI = 0.68–1.16). A sensitivity analysis using three-month periods and a complementary analysis adding completed suicides for case definition showed consistent results.

Conclusion: Compared with the general population, a lower risk of suicide attempt was observed among patients exposed to isotretinoin and there was no evidence for a triggering effect of isotretinoin initiation on suicide attempt. A selection of patients at lower risk for suicidal behaviour and appropriate treatment management could explain these findings. Risk management plans should therefore be maintained.

Key words: Acne, isotretinoin, suicide attempt, suicide, standardized incidence ratio, case-time-control analysis

Key Messages

- Isotretinoin is the only effective treatment for severe acne. An isotretinoin-related suicide risk is still debated and under scrutiny by regulatory agencies.
- We adressed two questions. What is the relative risk of suicide attempt observed among patients under isotretinoin, a major drug for severe acne? Is there a triggering effect of isotretinoin initiation on suicide attempt?
- In a French population-based analysis of more than 400 000 patients exposed to isotretinoin, standardized incidence ratios for suicide attempt were significantly lower than one, during, before or after isotretinoin treatment; and no significant triggering effect for suicide attempt was detected in the 2 or 3 months after isotretinoin initiation.
- These unexpected but fairly reassuring findings suggest that isotretinoin users are selected by prescribers, and well managed, from the perspective of suicidal behaviour. Risk management plans should however be maintained.

Introduction

Acne is a highly prevalent inflammatory skin disorder, affecting 90% of adolescents to varying degrees and it is severe in about 12–28% of cases.[1–5] Acne is still highly prevalent in adulthood, in generally less severe forms.[6–9]

Oral isotretinoin is a remarkably efficacious treatment for severe acne, providing clinical cure for more than 85% of patients after a course of 6 months on average.[10–15] Isotretinoin is recommended as a first-line treatment in severe cases, and as a second- or third-line treatment for resistant cases.[16–20]

Two main safety issues have been acknowledged for this treatment: a well-established teratogenicity,[21] leading to pregnancy prevention plans in several countries,[22–24] and a controversial risk of isotretinoin-induced psychiatric disturbances, with a special emphasis on suicide risk, leading to risk minimization measures among healthcare professionals and towards the public.[25–28] Concerning suicide risk, suicides and suicide attempts (SAs) occurring soon after isotretinoin initiation in 'healthy' subjects have attracted media attention. The issue of a risk of suicidal behaviour via a triggering effect in the weeks following isotretinoin initiation is partly supported by data from the Food and Drug Administration covering an 18 year post-marketing period and published in 2001 (reports of 85 subjects under isotretinoin hospitalized for depression, suicide ideation or SA within a median time of 1 month after treatment initiation).[29] There are likewise case reports of SA occurring mainly within the 2 months following the initiation of oral isotretinoin.[30]

Acne can itself induce psychological disorders[31–38] and the links between severe acne, isotretinoin, psychiatric disturbances and SA are particularly complex to disentangle (Supplementary Text 1 and Supplementary Figure 1, available as Supplementary data at *IJE* online, pages 2–4).

Several epidemiological approaches have been developed to study isotretinoin-related suicide risk and psychological disorders.[39–43] The most important study to date focused on suicide and SA and tried to distinguish the respective roles of acne and isotretinoin on a temporal basis.[43] The authors identified an increased risk for SA under isotretinoin, and also before isotretinoin initiation, clearly pointing to the difficulty of establishing a causal relationship between isotretinoin and suicidal behaviour after treatment initiation. This study, published in 2010, was based on prescription data from the 1980s, a period when the suspicion of isotretinoin-induced suicidal behaviour had not been widely raised. Today's awareness of this issue could substantially alter epidemiological data.

Our objective was to assess the risk of SA under isotretinoin on a large scale, at a time when awareness of this potential isotretinoin-induced risk is widely shared among regulatory authorities, physicians and patients. Specifically, we addressed the following two questions. Compared with the general population, is there a higher incidence of SA among subjects exposed to isotretinoin? Is there a triggering effect of isotretinoin initiation on SA?

Methods

Data sources

We used the French National Health Insurance database (SNIIRAM, Système National d'Information Inter-régimes de l'Assurance Maladie), which covers 98% of the 66-million French population.[44,45] The SNIIRAM database contains anonymous and individual data on demographic characteristics (gender, date of birth, date of death), all medical reimbursements including drugs and their date of issue, laboratory tests, outpatient medical care and visits, all hospitalizations and their associated diagnostic codes from the International Classification of Diseases, 10th Revision (ICD-10).

Access authorizations

The study protocol was authorized and approved by the French Drug Regulatory Agency (ANSM, Agence Nationale de Sécurité du Médicament) on 22 July 2016, by the National Institutional Review Board (INDS, Institut National des Données de Santé) and by the French data protection authority (CNIL, Commission Nationale de l'Informatique et des Libertés). Direct access to the whole database was granted by ANSM to our research consortium.

Selection criteria

Selected subjects were patients aged of 10–50 years with at least one initiation of a course of oral isotretinoin between 1 January 2009 and 31 July 2016. This population is referred to as the 'isotretinoin population'.

Exposure to isotretinoin

All isotretinoin issues were taken into account and identified using the Anatomical, Therapeutics and Chemical classification (ATC) code: D10BA01. In France, isotretinoin treatment prescription is renewed on a monthly basis. A course of isotretinoin was considered as discontinued if no issue occurred within 4 months following a given issue. All courses of isotretinoin initiated between 1 January 2009 and 31 July 2016 were considered. A patient was considered as exposed to isotretinoin from the date of course initiation to the 30th day after the last issue in the same course.

Details on criteria for selecting participants and on exposure are presented in Supplementary Text 2, available as Supplementary data at *IJE* online (page 5).

Outcomes

The main outcome was hospitalized SA, identified through the hospital discharge codes from ICD-10, X60.x to X69.x, X70.x to X79.x and X80.x to X84.x. The date of admission was used as the date of event. ICD-10 codes are presented in detail in Supplementary Table 1, available as Supplementary data at *IJE* online (page 6).

Statistical analyses

To assess the risk of SA, two analyses were conducted. (i) Computation of standardized incidence ratios (SIRs) comparing the observed number of SAs in the isotretinoin population with the expected number according to those observed in the general population. (ii) Detection of any isotretinoin initiation-related triggering effect on SA, using a case-time-control design.

Risk of SA analysed using standardized incidence ratios

The risk for suicidal behaviour was estimated using hospitalized SAs in the population exposed to isotretinoin, within different time frames: we used SIRs calculated for the periods before, during and after the courses of isotretinoin. Standardization was performed on age, gender, month and calendar year. Incidence rates for SA were computed in the SNIIRAM population and these rates were projected on the isotretinoin population to obtain a number of 'expected' SAs. All SAs observed between 1 January 2009 and 31 July 2016 were used to compute

SIRs. SIRs ('observed' over 'expected') for each period in relation to the courses of isotretinoin were computed using the STDRATE Procedure of the SAS/STAT software (SAS Institute, Inc., USA).

Detection of an isotretinoin initiation-related triggering effect on SA: case-time-control analysis

To study whether an initiation of isotretinoin could increase the risk of SA within the 2 months following initiation ('triggering effect'), we used a case-time-control design, in which each SA case was his/her own control. Two periods before the date of SA were screened for isotretinoin initiation: a risk period (0–60 days before the SA) and a control period (60–120 days before the SA). Each SA case counted for a yes/no exposure in both the risk and the control period. The case-time-control analysis included a selection of controls matched to SA cases to take the seasonal pattern observed for isotretinoin initiations into account (justification provided in Supplementary Table 2, available as Supplementary data at *IJE* online, page 7).[46] Each SA case was matched for age and gender to ten controls without SA, randomly selected from the isotretinoin population. The date of SA was used as the index date for the matched controls. Risk and control periods, as defined above, were screened for isotretinoin initiation among the controls, in the same way as for the cases, and a case-crossover odds ratio for controls was computed. The case-time-control odds ratio and its CI were estimated with a conditional logistic model, considering the interaction term between the exposure of interest (isotretinoin initiation) and the subject's group designation (SA case or control). Intuitively, the case-time-control odds ratio was the ratio of the case-crossover odds ratios obtained from SA cases and controls. All SAs from 1 January 2010 (1 year of historical records required) to 31 July 2016 were considered in the analysis. Subgroup analyses were conducted according to gender, age group (<20 years, 20–25 years, 25–50 years), history of psychiatric disorders and history of SA, as defined in Supplementary Text 3 and Supplementary Table 3, available as Supplementary data at *IJE* online (page 8). This analysis was performed using the LOGISTIC Procedure (with a STRATA option) on SAS/STAT software (SAS Institute, Inc., USA).

The populations defined above and the overall analytical framework are presented in Figure 1.

Completed suicides were added to SAs to perform a complementary analysis. Details are presented in Supplementary Text 4 and Supplementary Table 4, available as Supplementary data at *IJE* online (pages 9–10).

An a posteriori power calculation for the case-crossover analysis for SA cases is presented in Supplementary Table 5, available as Supplementary data at *IJE* online (page 11).

Results

What are the characteristics of isotretinoin patients and their courses of isotretinoin in France?

Over the study period, in France, 443 814 patients received at least one initiation of a course of oral isotretinoin, amounting to 244 154 person-years under isotretinoin. Half of them were <20 years old and 55% were males.

The main characteristics of the courses of isotretinoin were in line with what could be expected: a majority of treatments were initiated by a dermatologist (77.3%), the median course duration was 5.9 months (interquartile range 2.7–7.9 months) and 81.2% of patients had a single observable course of isotretinoin.

Two descriptive features were striking: an age distribution at isotretinoin initiation differing between males and females (Figure 2A), and autumn as a privileged season for initiating isotretinoin (Figure 2B).

At the time of their first observable course of isotretinoin, 12% of patients had one of our prelisted features pointing to an overt or possible psychological disturbance within the past 12 months, including use of anxiolytics for 8.7%, use of psychotropic medication for 4.8%, a history of long-term psychiatric illness for 1.8%, a history of hospitalization for a psychiatric disorder for 1% and a history of hospitalization for SA for 0.1%.

The main characteristics of the patients and the courses are presented in Table 1. The numbers of initiations per year, gender and age group are presented in Supplementary Table 6, available as Supplementary data at *IJE* online (page 12). The distribution of psychiatric history among a sample selected in the general population and isotretinoin population is presented in the Supplementary data (Supplementary Text 6, Supplementary Tables 7 and 8, available as Supplementary data at *IJE* online, pages 13–14).

Compared with the general population, do people under isotretinoin exhibit a higher risk for SA?

Compared with the general population, the overall risk during treatment was markedly lower, with an SIR for SA of 0.6 (95% CI = 0.53–0.67). SIRs were <1 in the years preceding the course of isotretinoin, ranging from 0.78–0.82, as well as in the years following the course of

Figure 1. Study populations and analytical framework.

isotretinoin, ranging from 0.87–0.78 (Figure 3A). Using a 2-month time frame before and during treatment, a declining trend was observed under treatment (Figure 3B).

These findings and trends were observed, with some minor differences, in almost all age categories and in both genders (Supplementary Figure 2, available as Supplementary data at *IJE* online, page 13). The incidence rate of SA during isotretinoin treatment was 9.1 for 100 000 person-years. The incidence rates of SA in the French population (the SNIIRAM population) are presented in Supplementary Figures 3–5, available as Supplementary data at *IJE* online (pages 15–17).

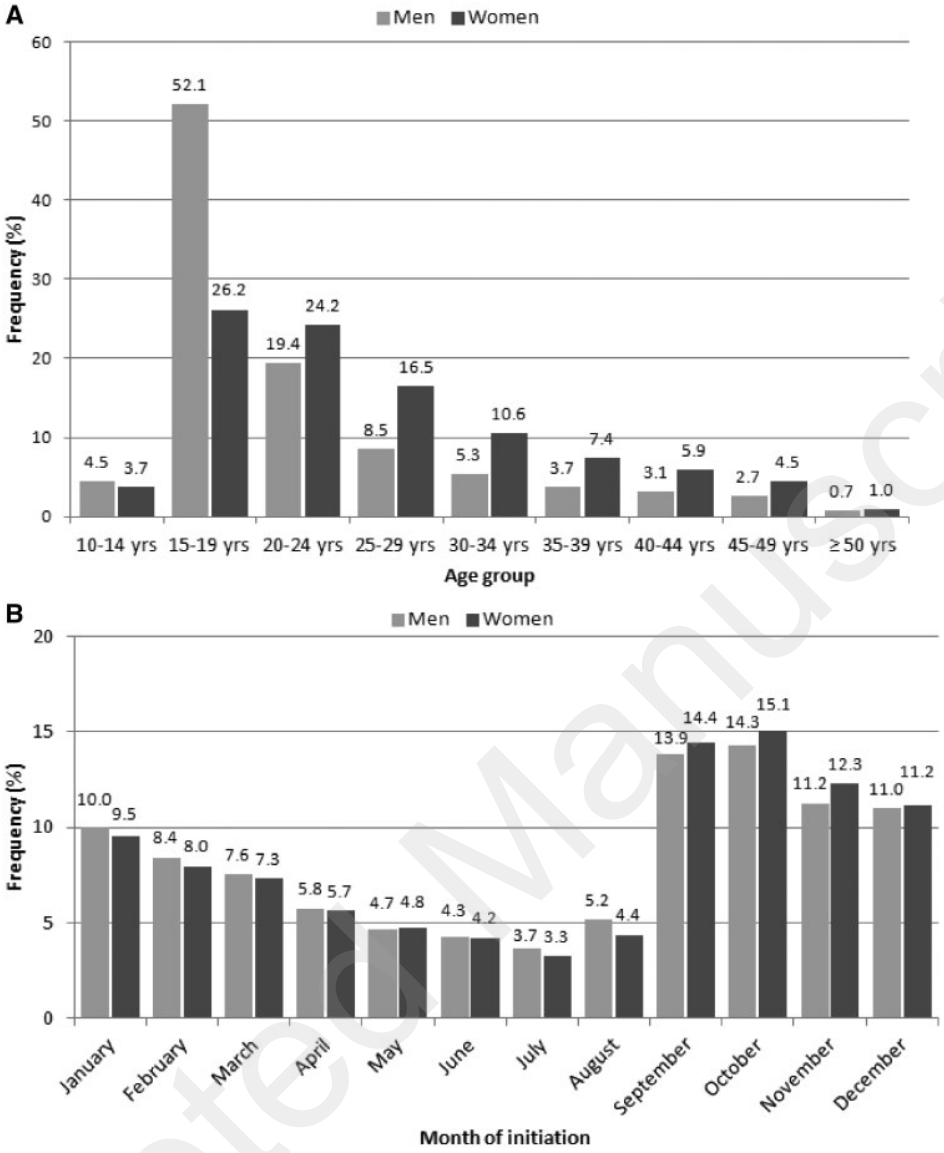

Figure 2. Descriptive characteristics at isotretinoin initiation. A, Age distribution by gender; B, calendar month for course initiation, by gender.

Was any triggering effect of isotretinoin initiation observed for SA?

The characteristics of the subjects included in the case-time-control analysis are presented in Supplementary Table 9, available as Supplementary data at *IJE* online (page 18). Among a total of 3954 cases of SA in the isotretinoin population, we observed 108 initiations in the risk period (0–2 months before the date of SA) vs 127 initiations in the control period (2–4 months before the date of SA); among 39 540 controls, we observed 1199 and 1253 initiations in the risk and control periods respectively. This yielded a case-time-control odds ratio of 0.89 (95% CI = 0.68–1.16).

Neither the analyses broken down into age and gender categories, nor a past history of SA or psychiatric disturbance, gave any clue for a marked or coherent contrasted result in any of the subgroups. The highest odds ratios were observed in the two following subgroups: men <20 years old and women aged 20–25 years (Figure 4). The results of the case-time-control analysis in the sensitivity analysis using 3-month periods [odds ratio of 0.82 (95% CI = 0.66–1.02)], including results in the subgroups, were not substantially different from the main analysis (Figure 5).

In the complementary analysis on the 2010–2014 study period, in which we incorporated SAs and completed suicides, 3200 cases (i.e. either SA or completed suicide) were recorded. We observed 110 initiations in the risk period (0–2 months before the date of the event) vs 124 initiations in the control period (2–4 months before the date of the event);

Table 1. Characteristics of isotretinoin patients and courses of isotretinoin

	Men *n* = 244 422 (318 742 courses)	Women *n* = 199 392 (249 150 courses)	Overall *n* = 443 814 (567 892 courses)
Number of person-years			
Total	1 852 359	1 511 666	3 364 024
Under treatment	135 170	108 984	244 154
Age at first observed course of isotretinoin			
<20 yrs, *n* (%)	149 437 (61.1)	63 011 (31.6)	212 448 (47.9)
20–25 yrs, *n* (%)	47 546 (19.5)	55 404 (27.8)	102 950 (23.2)
>25 yrs, *n* (%)	47 439 (19.4)	80 977 (40.6)	128 416 (28.9)
Mean (SD)	21.2 (7.8)	25.5 (9.0)	23.1 (8.6)
Median (IQR)	18.0 (16.0; 23.0)	23.0 (18.0; 31.0)	20.0 (17.0; 27.0)
Number of courses observed			
1 course, *n* (%)	196 004 (80.2)	164 467 (82.5)	360 471 (81.2)
2 courses, *n* (%)	33 922 (13.9)	26 159 (13.5)	60 081 (13.5)
3 courses *n* (%)	8729 (3.6)	5643 (28)	14 372 (3.2)
4 courses or more, *n* (%)	5767 (2.4)	3123 (1.6)	8890 (2.0)
Mean (SD)	1.3 (0.8)	1.2 (0.7)	1.3 (0.7)
Median (IQR)	1.0 (1.0; 1.0)	1.0 (1.0; 1.0)	1.0 (1.0; 1.0)
Age at course initiation			
<20 yrs, *n* (%)	180 358 (56.6)	74 330 (29.8)	254 688 (44.9)
20–25 yrs *n* (%)	68 550 (21.5)	70 272 (28.2)	138 822 (24.5)
>25 yrs, *n* (%)	69 834 (21.9)	104 548 (42.0)	174 382 (30.7)
Mean (SD)	21.9 (8.3)	25.9 (9.2)	23.6 (8.9)
Median (IQR)	19.0 (17.0 ; 24.0)	24.0 (19.0 ; 31.0)	20.0 (17.0 ; 28.0)
Course duration			
≤30 days (single issue), *n* (%)	59 165 (20.3)	35 368 (15.7)	94 533 (18.3)
31–60 days (1–2 months), *n* (%)	7259 (2.5)	4766 (2.1)	12 025 (2.3)
61–90 days (2–3 months), *n* (%)	19 958 (6.8)	12 164 (5.4)	32 122 (6.2)
91–180 days (3–6 months), *n* (%)	70 474 (24.2)	55 826 (24.9)	126 300 (24.5)
181–270 days (6–9 months), *n* (%)	89 536 (30.7)	84 036 (37.4)	173 572 (33.6)
>270 days (>9 months), *n* (%)	45 209 (15.5)	32 520 (14.5)	77 729 (15.1)
Date of initiation or end not observable, *n*	27 141	24 470	51 611
Mean (SD), in months	5.6 (4.0)	5.9 (3.5)	5.8 (3.8)
Median (IQR), in months	5.7 (2.2 ; 7.9)	6.1 (3.2 ; 7.9)	5.9 (2.7 ; 7.9)
Cumulate dose per course (mg)			
Mean (SD)	4814 (3621)	5117 (3285)	4946 (3482)
Median (IQR)	4350 (1500; 7500)	5400 (2250; 7350)	4800 (1800; 7350)
Daily dose[a] (mg)			
Mean (SD)	29 (14)	30 (13)	29 (14)
Median (IQR)	29 (20; 37)	29 (21; 36)	29 (20; 37)
Treatment delivered			
CURACNE$^{(R)}$, *n* (%)	189 307 (59.4)	151 216 (60.7)	340 523 (60.0)
PROCUTA$^{(R)}$, *n* (%)	100 417 (31.5)	74 250 (29.8)	174 667 (30.8)
CONTRACNE$^{(R)}$, *n* (%)	14 326 (4.5)	12 836 (5.2)	27 162 (4.8)
ACNETRAIT$^{(R)}$, *n* (%)	14 581 (4.6)	10 751 (4.3)	25 332 (4.5)
Other, *n* (%)	111 (0.03)	97 (0.04)	208 (0.03)
Type of prescriber			
Dermatologist, *n* (%)	242 339 (76.0)	196 701 (79.0)	439 040 (77.3)
General practitioner, *n* (%)	59 481 (18.7)	39 290 (15.8)	98 771 (17.4)
Other, *n* (%)	16 922 (5.3)	13 159 (5.3)	30 081 (5.3)
Psychiatric history[b], *n* (%)	24 767 (8.8)	37 115 (16.8)	61 882 (12.3)
Long-term psychiatric illness[c], *n* (%)	4738 (1.7)	4183 (1.9)	8921 (1.8)
Hospitalization for SA[d], *n* (%)	224 (0.1)	407 (0.2)	631 (0.1)

(Continued)

Table 1. Continued

	Men $n = 244\,422$ (318 742 courses)	Women $n = 199\,392$ (249 150 courses)	Overall $n = 443\,814$ (567 892 courses)
Hospitalization in medical or surgical unit for psychiatric disorder[e], *n* (%)	1891 (0.7)	1713 (0.8)	3604 (0.7)
Hospitalization in psychiatry unit, n (%)	897 (0.3)	805 (0.4)	1702 (0.3)
Psychotropic treatment[f], *n* (%)	10 111 (3.6)	16 158 (7.3)	26 269 (5.2)
Anxiolytic treatment[f], *n* (%)	15 692 (5.6)	28 169 (12.7)	43 861 (8.8)
Other psychiatric history, *n* (%)	5479 (2.0)	10 433 (4.7)	15 912 (3.2)
No other psychiatric history, *n* (%)	10 213 (3.6)	17 736 (8.0)	27 949 (5.6)

[a]Cumulative dose per course divided by the duration of the course (in days).
[b]In the 12 months preceding isotretinoin initiation.
[c]Irrespective of the date of the onset of the illness.
[d]SA defined using the diagnostic codes of the International Classification of Diseases 10th revision listed in Supplementary Table 1, available as Supplementary data at *IJE* online.
[e]Psychiatric disorder defined using the diagnostic codes of the International Classification of Diseases 10th revision listed in Supplementary Text 3 and Table 3, available as Supplementary data at *IJE* online.
[f]Psychotropic and anxiolytic treatments defined using the anatomical, therapeutic and chemical classification codes, listed in Supplementary Text 3, available as Supplementary data at *IJE* online.
n, number of patients with at least one course of isotretinoin; yrs, years; SD, standard deviation; IQR, interquartile range; SA, suicide attempt.

among the 32 000 controls, we observed 1135 initiations in the risk period and 1116 initiations in the control period. This yielded a case-time-control value of 0.87 (95% CI = 0.67–1.14). The analysis using 3-month periods was also in line with this result (Supplementary Table 10, available as Supplementary data at *IJE* online, page 20).

Discussion

Using French nationwide exhaustive reimbursement data from recent years, we found that patients under isotretinoin exhibited a lower risk of SA while they were under treatment, but also before and after their treatment course. In addition, we found no evidence for an isotretinoin-triggered risk for SA in the first weeks after treatment initiation.

These results have shed new light on the long-standing issue of potentially isotretinoin-induced suicidal behaviour among acne patients. The suspicion of an isotretinoin-related risk for suicidal behaviour, and more generally for psychological disturbances, has prompted drug regulatory agencies in the USA,[25] Europe,[26–28] and elsewhere,[47] to release specific warnings. To date, the most robust published epidemiological data has stemmed from a 2010 study report showing that the risk of SA was increased under isotretinoin, but also that the start of this increase was detectable before treatment initiation. This pre-isotretinoin risk was logically attributed to severe acne itself.[43] Our analysis of the SIRs for SAs, using a similar approach, is in stark contrast with this previous report. Importantly, the 2010 study referred to isotretinoin prescriptions dating back to the 1980s, at a time where the risk associated with isotretinoin was not focused on psychological disturbances. Regarding the SIRs of <1 observed in our isotretinoin population, we hypothesize that the awareness of a potential risk among isotretinoin prescribers is the main determinant of our results, through patient selection (depletion of susceptible subjects) at treatment initiation and increased attention to psychological changes and disorders during isotretinoin treatment. Patient selection could have led to higher-risk patients being excluded from isotretinoin prescriptions. This would account for the before- and after-treatment SIRs being significantly <1. Removal of the acne-related share of the risk as a result of therapeutic efficacy could also have contributed,[31–34,38,48] but this would not account for an after-treatment SIR returning to the same level as the before-treatment ratio. A direct comparison between the isotretinoin population and the French general population regarding psychiatric history was not feasible for both technical and regulatory reasons. However, descriptive characteristics in a 1% sample of the general population, focused on psychiatric history, are provided as Supplementary Data, available as Supplementary data at *IJE* online.

High-impact press releases in the media have pointed to the idea that some SAs or suicides could occur like a clap of thunder in a calm sky soon after isotretinoin initiation. Our nested case-time-control analysis was designed to address this issue. It was worth specifically investigating a 'triggering effect' of this nature, since the selection of patients at lower risk for suicidal behaviour mentioned above would not circumvent this risk. Although we used a method specifically designed to determine whether isotretinoin could trigger a SA in the 2 months after initiation, we

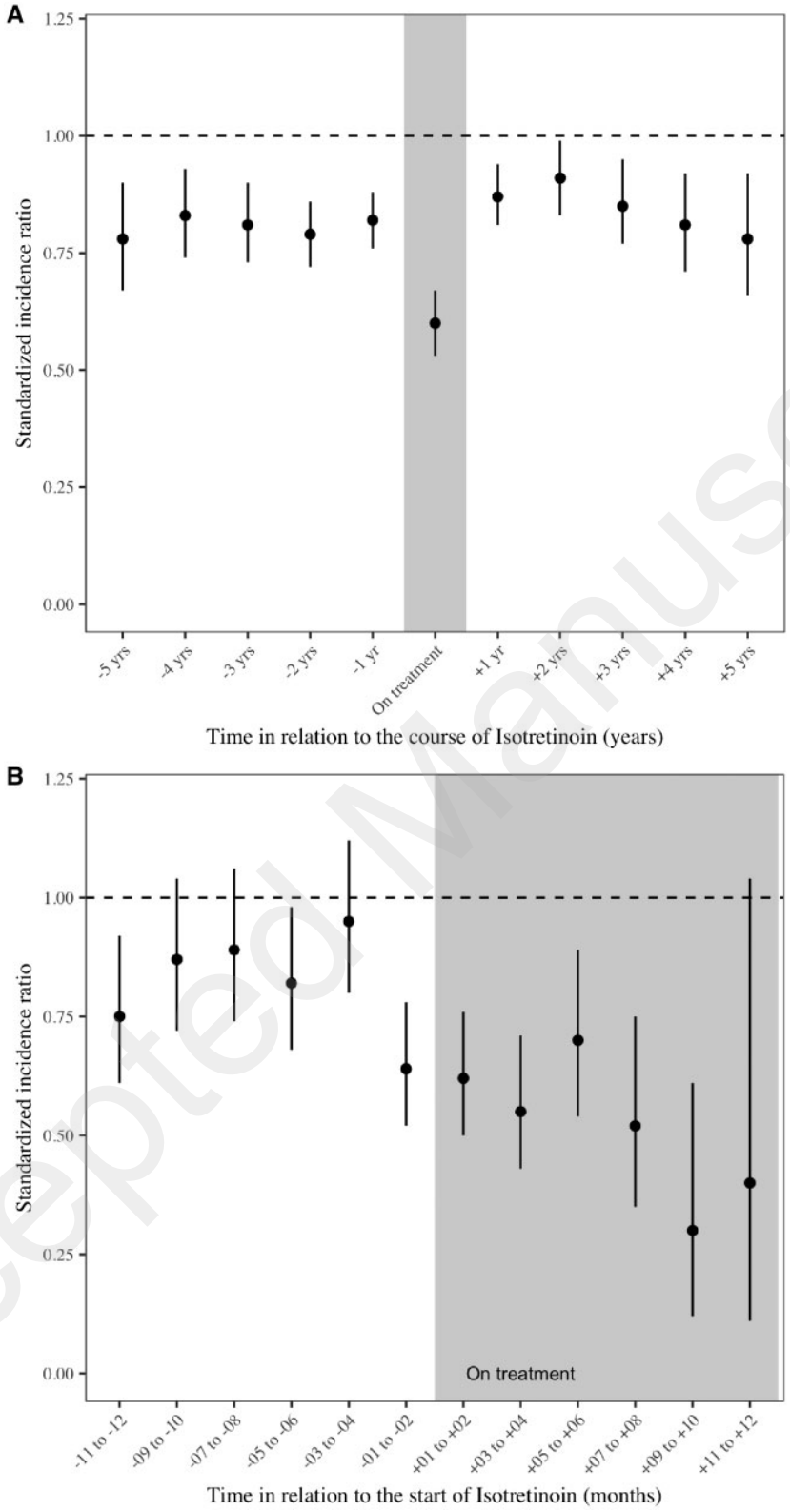

Figure 3. Standardized incidence ratios (SIRs) for suicide attempt. A, SIRs per one-year period, during, in the 5 years before, and in the 5 years after isotretinoin treatment; B, SIRs per 2-month periods during, in the one year before, and in the one year after isotretinoin treatment.

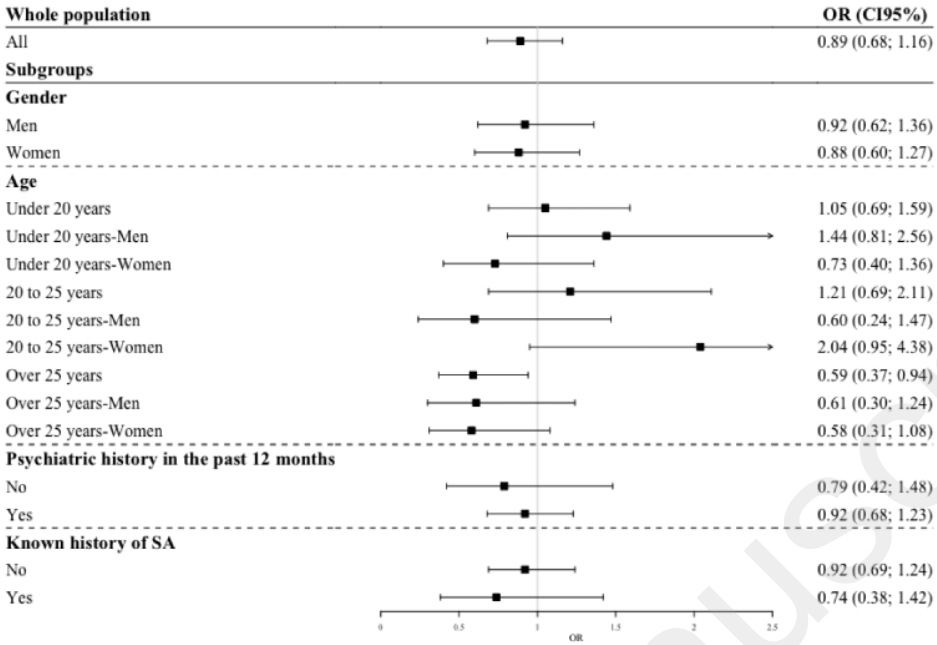

Figure 4. Results of the case-time-control analysis. The analysis was conducted over 2-month periods and according to gender, age group (<20 years, 20–25 years, 25–50 years), psychiatric history in the 12 months preceding the suicide attempt and known history of suicide attempt.

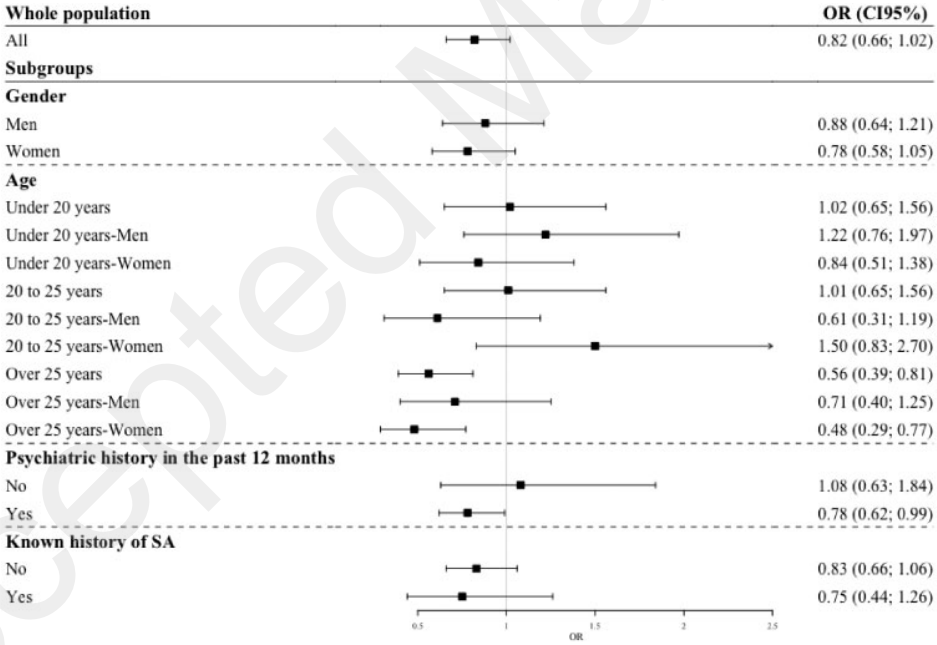

Figure 5. Results of the case-time-control analysis over 3-month periods (sensitivity analysis) and according to gender, age group (<20 years, 20–25 years, 26–50 years), psychiatric history in the 12 months preceding the suicide attempt and known history of suicide attempt.

did not see evidence of any triggering effect. Without a precise pharmacological hypothesis on isotretinoin action on the central nervous system,[30,49,50] any choice of a temporal window for a triggering effect is debatable. Pre-planned sensitivity analyses using 3-month periods were in line with the main analysis. Shorter periods (e.g. 1 month) were not planned because of a higher risk of classification bias linked to the precise date of treatment initiation. In the subgroups of men <20 years old and women aged 20–25 years, no rationale seems able to explain these findings, which probably reflect random variations. A self-controlled design has the advantage of adjusting on

individual time-invariant confounders. The refinement of using a case-time-control design[46,51–54] was justified by the seasonality of isotretinoin initiation. Furthermore, because SA had a high incidence in our study population, we would not have been able to detect a causal and direct isotretinoin-induced effect on suicidal behaviours if such causal risk was restricted to a very small sub-population, defined for example by specific genetic polymorphisms.

On the issue of isotretinoin-related risk for psychological disturbances, confounding resulting from severe acne is an intractable difficulty that no design can fully take into account.[55–57] Severe acne has an impact on psychological equilibrium.[31–37,48] Therefore, ideally, a control group with severe acne not treated with isotretinoin would be necessary. But isotretinoin is the one and only treatment for severe or treatment-resistant acne, and oral antibiotics, like cyclines, cannot be used as proxies for the same levels of severity. No previous study had circumvented this major obstacle of confounding by indication.[39–42] Various approaches have been used that do not directly compare with ours, because of their different designs and different outcomes. One study used a case-crossover design over a 12-month period during which acne severity would not be constant, and it analysed the prescription of antidepressants[42] and hospitalizations for depression. Finally, a common limitation to all previous studies is their limited power.

Our study has significant strengths. The SNIIRAM database guarantees an almost exhaustive nationwide coverage of 66 million people, with no attrition bias.[44] As already stated, the study was based on recent data. Certain limitations should however be discussed. First, the outcome was limited to hospitalized SAs. In practice, a stay of more than 8 hours in the emergency department leads to coding and recording. Although we had no access to SAs not reaching an emergency department or staying less than 8 hours, it is unlikely that these SAs would have a relationship with isotretinoin differing from those we studied. Second, our analysis was limited to SAs, while other potentially significant acute psychiatric events would also be worth studying, since there could be different pharmacological triggers. Third, although the overall power is high and our database is larger than any previously used,[42–43] the subgroup analyses may have been limited by suboptimal power.

Conclusion

Overall, although our results are reassuring, a causal association between isotretinoin and SA and suicide cannot be completely ruled out. As a general consequence, the current, supposedly prudent, prescribers' attitude should be maintained. Other large-scale epidemiological investigations in other settings and other countries could help substantiate the hypothesized link between patient selection and the absence of a general isotretinoin-related risk for SA. What is at stake is that patients having psychological disturbances alongside severe acne could be left untreated. Specific investigations should assess this potential downside.

Supplementary data

Supplementary data are available at *IJE* online.

Funding

This work was supported by a grant from the French National Agency for Medicines and Health Products Safety (Agence Nationale de Sécurité du Médicament - ANSM), France.

Acknowledgments

We thank Angela Verdier and Sarah Leyshon for the English language revision.

Conflict of interest: None declared.

References

1. White GM. Recent findings in the epidemiologic evidence, classification, and subtypes of acne vulgaris. *J Am Acad Dermatol* 1998;**39**:S34–37.
2. Law MP, Chuh AA, Lee A, Molinari N. Acne prevalence and beyond: acne disability and its predictive factors among Chinese late adolescents in Hong Kong. *Clin Exp Dermatol* 2010;**35**: 16–21.
3. Williams HC, Dellavalle RP, Garner S. Acne vulgaris. *Lancet* 2012;**379**:361–72.
4. Dawson AL, Dellavalle RP. Acne vulgaris. *BMJ* 2013;**346**: f2634.
5. Silverberg JI, Silverberg NB. Epidemiology and extracutaneous comorbidities of severe acne in adolescence: a U.S. population-based study. *Br J Dermatol* 2014;**170**:1136–42.
6. Cunliffe WJ, Gould DJ. Prevalence of facial acne vulgaris in late adolescence and in adults. *Br Med J* 1979;**1**:1109–10.
7. Goulden V, Stables GI, Cunliffe WJ. Prevalence of facial acne in adults. *J Am Acad Dermatol* 1999;**41**:577–80.
8. Collier CN, Harper JC, Cafardi JA *et al*. The prevalence of acne in adults 20 years and older. *J Am Acad Dermatol* 2008;**58**: 56–59.
9. Bhate K, Williams HC. Epidemiology of acne vulgaris. *Br J Dermatol* 2013;**168**:474–85.
10. Peck GL, Olsen TG, Yoder FW *et al*. Prolonged remissions of cystic and conglobate acne with 13-cis-retinoic acid. *N Engl J Med* 1979;**300**:329–33.
11. Peck GL, Olsen TG, Butkus D *et al*. Isotretinoin versus placebo in the treatment of cystic acne. A randomized double-blind study. *J Am Acad Dermatol* 1982;**6**:735–45.

12. Jones H, Blanc D, Cunliffe WJ. 13-cis retinoic acid and acne. *Lancet* 1980;**2**:1048–49.
13. Jones DH, King K, Miller AJ, Cunliffe WJ. A dose-response study of I3-cis-retinoic acid in acne vulgaris. *Br J Dermatol* 1983;**108**:333–43.
14. Jones DH, Cunliffe WJ. Remission rates in acne patients treated with various doses of 13-cis-retinoic acid (isotretinoin). *Br J Dermatol* 1984;**111**:123–25.
15. Strauss JS, Rapini RP, Shalita AR *et al*. Isotretinoin therapy for acne: results of a multicenter dose-response study. *J Am Acad Dermatol* 1984;**10**:490–96.
16. Le Cleach L, Lebrun-Vignes B, Bachelot A *et al*. French Acne Guidelines Working Group and Centre of Evidence of Dermatology. Guidelines for the management of acne: recommendations from a French multidisciplinary group. *Br J Dermatol* 2017;**177**:908–13.
17. Haute Autorité de Santé: Practice Guideline on the Treatment of Acne. 2015. http://www.sfdermato.com/media/pdf/recommandation/acne-reco-4b963af7b7ece256f3da65f256447e32.pdf (22 January 2019, date last accessed)
18. Nast A, Dréno B, Bettoli V *et al*. European evidence-based (S3) guideline for the treatment of acne—update 2016—short version. *J Eur Acad Dermatol Venereol* 2016;**30**:1261.
19. Zaenglein AL, Pathy AL, Schlosser BJ *et al*. Guidelines of care for the management of acne vulgaris. *J Am Acad Dermatol* 2016;**74**:945–73.e33.
20. Roman CJ, Cifu AS, Stein SL. Clinical guidelines for management of acne vulgaris-reply. *JAMA* 2017;**317**:213.
21. Rosa FW. Teratogenicity of isotretinoin. *Lancet* 1983;**2**:513.
22. U.S. Food and Drug Administration (FDA). *The iPLEDGE Program Guide To Best Practices For Isotretinoin*. https://www.ipledgeprogram.com/Documents/Patient%20Intro%20Broch_092015.pdf (22 January 2019, date last accessed).
23. Agence Nationale de Sécurité des Médicaments et des produits de santé (ANSM), Pregnancy Prevention Programme. http://ansm.sante.fr/S-informer/Points-d-information-Points-d-information/Isotretinoine-orale-et-grossesse-Actualisation-des-documents-destines-aux-professionnels-de-sante-pour-la-minimisation-des-risques-Point-d-information (22 January 2019, date last accessed).
24. GOV.UK. *Drug Safety Update Vol 6, Issue 11 June* 2013*: H1, Pregnancy Prevention Programme*. https://www.gov.uk/drug-safety-update/oral-retinoids-pregnancy-prevention-reminder-of-measures-to-minimise-teratogenic-risk (22 January 2019, date last accessed).
25. U.S. Food and Drug Administration (FDA). Medication Guide, Revised in January 2010. https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/018662s061MedGuide.pdf (22 January 2019, date last accessed).
26. Agence Nationale de Sécurité des Médicaments et des produits de santé (ANSM). Medication Guide of Risk Minimization Measures, *September,* 2015. http://ansm.sante.fr/var/ansm_site/storage/original/application/60aa4def169fb548f5c2f54541857aae.pdf (22 January 22, date last accessed).
27. GOV.UK. *Guidance, Isotretinoin for Severe Acne: Uses and Effects, December 18,* 2014. https://www.gov.uk/government/publications/isotretinoin-for-severe-acne-uses-and-effects/isotretinoin-for-severe-acne-uses-and-effects#further-information (22 January 2019, date last accessed).
28. GOV.UK. *Public Assessment Review, November* 2014. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/391670/isotretinoin_and_psychiatric_disorders_PAR_Final_web.pdf (22 January 2019, date last accessed).
29. Wysowski DK, Pitts M, Beitz J. An analysis of reports of depression and suicide in patients treated with isotretinoin. *J Am Acad Dermatol* 2001;**45**:515–19.
30. Bremner JD, Shearer KD, McCaffery PJ. Retinoic acid and affective disorders: the evidence for an association. *J Clin Psychiatry* 2012;**73**:37–50.
31. Gupta MA, Gupta AK. Depression and suicidal ideation in dermatology patients with acne, alopecia areata, atopic dermatitis and psoriasis. *Br J Dermatol* 1998;**139**:846–50.
32. Purvis D, Robinson E, Merry S, Watson P. Acne, anxiety, depression and suicide in teenagers: a cross-sectional survey of New Zealand secondary school students. *J Paediatr Child Health* 2006;**42**:793–96.
33. Dalgard F, Gieler U, Holm JØ, Bjertness E, Hauser S. Self-esteem and body satisfaction among late adolescents with acne: results from a population survey. *J Am Acad Dermatol* 2008;**59**:746–51.
34. Halvorsen JA, Stern RS, Dalgard F, Thoresen M, Bjertness E, Lien L. Suicidal ideation, mental health problems, and social impairment are increased in adolescents with acne: a population-based study. *J Invest Dermatol* 2011;**131**:363–70.
35. Misery L. Consequences of psychological distress in adolescents with acne. *J Invest Dermatol* 2011;**131**:290.
36. Gupta MA, Gupta AK, Vujcic B. Increased frequency of Attention Deficit Hyperactivity Disorder (ADHD) in acne versus dermatologic controls: analysis of an epidemiologic database from the US. *J Dermatolog Treat* 2014;**25**:115–18.
37. Misery L, Wolkenstein P, Amici J-M *et al*. Consequences of acne on stress, fatigue, sleep disorders and sexual activity: a population-based study. *Acta Derm Venereol* 2015;**95**:485–88.
38. Ramrakha S, Fergusson DM, Horwood LJ *et al*. Cumulative mental health consequences of acne: 23-year follow-up in a general population birth cohort study. *Br J Dermatol* 2016;**175**:1079–81.
39. Jick SS, Kremers HM, Vasilakis-Scaramozza C. Isotretinoin use and risk of depression, psychotic symptoms, suicide, and attempted suicide. *Arch Dermatol* 2000;**136**:1231–36.
40. Hersom K, Neary MP, Levaux HP, Klaskala W, Strauss JS. Isotretinoin and antidepressant pharmacotherapy: a prescription sequence symmetry analysis. *J Am Acad Dermatol* 2003;**49**:424–32.
41. Friedman T, Wohl Y, Knobler HY *et al*. Increased use of mental health services related to isotretinoin treatment: a 5-year analysis. *Eur Neuropsychopharmacol* 2006;**16**:413.
42. Azoulay L, Blais L, Koren G, LeLorier J, Bérard A. Isotretinoin and the risk of depression in patients with acne vulgaris: a case-crossover study. *J Clin Psychiatry* 2008;**69**:526–32.
43. Sundström A, Alfredsson L, Sjölin-Forsberg G, Gerdén B, Bergman U, Jokinen J. Association of suicide attempts with acne and treatment with isotretinoin: retrospective Swedish cohort study. *BMJ* 2010;**341**:c5812.
44. Tuppin P, Rudant J, Constantinou P *et al*. Value of a national administrative database to guide public decisions: from the système national d'information interrégimes de l'Assurance Maladie (SNIIRAM) to the système national des données de santé (SNDS) in France. *Rev Epidemiol Sante Publique* 2017;**65**:S149–67.

45. Palmaro A, Moulis G, Despas F, Dupouy J, Lapeyre-Mestre M. Overview of drug data within French health insurance databases and implications for pharmacoepidemiological studies. *Fundam Clin Pharmacol* 2016;**30**:616–24.
46. Suissa S. The case-time-control design. *Epidemiology* 1995;**6**:248–53.
47. Australian Government. *Therapeutic Goods Administration. Medicines Safety Update, Volume 7, Number 4, August 2016*. https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf? OpenAgent&id=CP-2012-CMI-01864-3 (22 January 2019, date last accessed).
48. Huang YC, Cheng YC. Isotretinoin treatment for acne and risk of depression: a systematic review and meta-analysis. *J Am Acad Dermatol* 2017;**76**:1068–76.e9.
49. Bremner JD, Fani N, Ashraf A. Functional brain imaging alterations in acne patients treated with isotretinoin. *AJP* 2005;**162**:983–91. Erratum in: *Am J Psychiatry* 2008;165:1614
50. Bremner JD, McCaffery P. The neurobiology of retinoic acid in affective disorders. *Prog Neuropsychopharmacol Biol Psychiatry* 2008;**32**:315–31.
51. Schneeweiss S, Stürmer T, Maclure M. Case-crossover and case-time-control designs as alternatives in pharmacoepidemiologic research. *Pharmacoepidemiol Drug Saf* 1997;**6**:S51–59.
52. Suissa S. The case-time-control design: further assumptions and conditions. *Epidemiology* 1998;**9**:441–45.
53. Maclure M, Mittleman MA. Should we use a case-crossover design? *Annu Rev Public Health* 2000;**21**:193–221.
54. Wang PS, Schneeweiss S, Glynn RJ, Mogun H, Avorn J. Use of the case-crossover design to study prolonged drug exposures and insidious outcomes. *Ann Epidemiol* 2004;**14**:296–303.
55. Bigby M. Does isotretinoin increase the risk of depression? *Arch Dermatol* 2008;**144**:1197–99. discussion 1234-5.
56. Langan SM, Batchelor JM. Acne, isotretinoin and suicide attempts: a critical appraisal. *Br J Dermatol* 2011;**164**:1183–85; discussion 1185–86.
57. Margolis DJ. Commentary: acne, isotretinoin and suicide attempts. *Br J Dermatol* 2011;**164**:1186–87.