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Accepted Article

Isotretinoin is the mainstay of treatment for severe acne, often proposed as a second-line treatment after tetracyclines¹. While severe acne is associated with psychological disturbances², isotretinoin itself has been suspected to induce psychological side-effect, although strong evidence is lacking^{3,4}. In a recent French nationwide study, we surprisingly evidenced lower standardized incidence ratios for suicide attempt in subjects treated with isotretinoin compared to the general population⁵. These findings could stem from the reluctance to prescribe isotretinoin in patients with a psychiatric background, because of an alleged additional risk associated with isotretinoin in these patients. To investigate this hypothesis, we conducted a population-based study to investigate whether among patients with an identified psychiatric history, isotretinoin was less frequently initiated, compared to patients without psychiatric history.

This study was conducted using the Echantillon Généraliste des Bénéficiaires (EGB), which is a 1/97th representative sample of the French health care insurance system database⁶. We included patients aged from 15 to 25 years old, who received at least one tetracycline course for acne from January 1, 2011, to December 31, 2018. Start of follow-up was the initiation of tetracyclines. Psychiatric history was assessed using hospitalizations data and psychotropic drug dispensations, at baseline and throughout follow-up. The primary endpoint was the time from baseline to isotretinoin initiation. Patients were censored at the time of death, exit from EGB or the end of the study. The Cox proportional hazards model was used to evaluate the association between psychiatric history and time to introduction of isotretinoin, using age as a time scale. Psychiatric history was analyzed as a time-dependent binary variable. All analyses were stratified on birth year. Analyses were conducted separately according to gender, because of different conditions of use of isotretinoin in women.

A total of 5532 men and 7029 women were included in the study. The population characteristics are presented in Table 1. A second-line systemic anti-acne therapy using isotretinoin was initiated for 679 men and 535 women. At baseline, 279 men (5%) and 500 women (7.1%) presented with a psychiatric history. In multivariate analysis, psychiatric history was associated with a longer time lapse to isotretinoin initiation after tetracycline initiation among women (HR 0.53, 0.35 – 0.82). Among men, the association was not significant but also suggested a delay in isotretinoin treatment for patients with a psychiatric history (HR 0.73, 0.5 - 1.1]). Low-income status and initial care by a non-dermatologist were also associated with a longer time lapse to isotretinoin initiation in both genders. Other variables showed non-significant association. The results are shown in Table 2. No statistical interaction between psychiatric history and covariates was evidenced.

The population-based design and the large sample are the two main strengths of our study. Age and gender, the two main confounders, were controlled for with age as the time scale in the Cox regression model and separate analyses according to gender. Some limitations should be discussed, however. The lack of clinical information on acne severity, and the low number socioeconomic indicators available in our database, could be responsible for residual confounding.

Our study demonstrates that patients with a psychiatric history are less readily treated with isotretinoin for their acne, especially among women. Several studies have demonstrated that severe acne is in itself associated with mental health issues^{2,7}. Reluctance to treat acne in this population could imply the perpetuation of the acne-related psychiatric morbidity, which would be alleviated with a highly efficacious anti-acne treatment such as isotretinoin⁸. When prescribing systemic therapy for severe acne in patients with psychiatric morbidity, the individual risk-benefit

ratio should be carefully assessed, and a careful follow-up should be implemented to assess changes.

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	Men	Women
Number, n	5 531	7 029
Age, y, mean (SD)	18.02 (2.7)	19.01 (3.1)
Low-income status, n (%)	691 (12.5)	1 038 (14.8)
Type of tetracycline, n (%)		
Doxycycline	4176 (75.5)	5355 (76.2)
Lymecycline	1270 (23)	1592 (22.6)
Minocycline	85 (1.5)	82 (1.2)
Claim system, n (%)		
General claim system	4 857 (87.8)	6 154 (87.6)
Others	674 (12.2)	875 (12.4)
Tetracycline prescriber, n (%)		
Dermatologist	2 611 (47.2)	3 535 (50.3)
Others	2 920 (52.8)	3 494 (49.7)
Tetracycline starting period, n (%)		
Autumn	1 591 (28.8)	2 022 (28.8)
Winter	1 738 (31.4)	2 139 (30.4)
Spring	1 358 (24.6)	1 734 (24.7)
Summer	844 (15.3)	1 134 (16.1)
Psychiatric history at baseline		
No	5 252 (95)	6 529 (92.9)
Yes	279 (5)	500 (7.1)

Table 1: Characteristics of the study population at cohort entry (first prescription of tetracycline for

acne). N: number, y: year, SD: standard deviation. The season at cohort entry was included in the analysis, given the seasonality of isotretinoin initiation.

	Women – Multivariate analysis		Men – Multivariate Analysis	
	HR	95% CI	HR	95% CI
Psychiatric history*	0.53	0.35 – 0.82	0.73	0.50 - 1.10
Low-income status	0.56	0.40 - 0.77	0.50	0.36 - 0.67
Initial prescriber				
Dermatologist	1		1	
Other	0.43	0.34 - 0.53	0.61	0.52 - 0.71
Tetracycline starting period				
Winter	1		1	
Spring	0.95	0.74 - 1.22	0.92	0.75 - 1.12
Summer	0.91	0.67 - 1.24	0.98	0.76 - 1.25
Autumn	1.05	0.83 - 1.34	1.05	0.87 - 1.28
Claim system				
General claim system	1		1	
Others	1.08	0.80 – 1.46	0.96	0.75 – 1.23

Table 2: Determinants of isotretinoin prescription. The risks are estimated using hazard ratios (HR) and confidence interval (CI) in multivariate analyses for women and men. HR were estimated with a Cox hazard model for time-dependent variables, with age as a time scale. HR lower than 1 indicates a longer time to isotretinoin initiation. *The reference class is absence of a psychiatric history.