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Isotretinoin use for acne is not associated with an increased risk of migraine, fibromyalgia, multiple sclerosis, or neuropathy: A matched, retrospective cohort study

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Keywords

isotretinoin; tetracycline; doxycycline; minocycline; migraine; fibromyalgia; multiple sclerosis; neurologic; adverse event

While the potential association between isotretinoin and mood disorders has been extensively evaluated,[1,2] little is known about whether isotretinoin may be associated with other neurologic adverse events. Based on case reports and the potential neurotoxicity of vitamin A and retinoids, concerns have been raised regarding whether isotretinoin may cause neurologic adverse effects such as migraines,[3] fibromyalgia, multiple sclerosis, and neuropathy.[4] These concerns are also commonly discussed on social media and online forums. However, studies designed to evaluate whether isotretinoin may be causally related to these potential neurologic adverse events are lacking.

Using a new-user, active comparator design with the Truven Health MarketScan Commercial Claims Database from January 1, 2017-December 31, 2020, this retrospective cohort study sought to compare the risk of developing migraine, fibromyalgia, multiple sclerosis, and neuropathy in patients with acne treated with isotretinoin versus tetracycline-class antibiotics (i.e., doxycycline, minocycline, sarecycline). The MarketScan database includes individuals from more than 160 large employers and health plans across the United States.

Patients were identified according to the following criteria: (1) at least 1 diagnosis of acne,[5] (2) a minimum of 60 days of treatment with isotretinoin or tetracycline-class antibiotic, (3) no prior encounters for the outcomes of interest, (4) no prior encounters for depression (F32.x, F33.x) or anxiety (F41.x, F42.x, F43.x) to reduce the risk of confounding by indication if isotretinoin is avoided in these populations. The cohorts were matched 1:1 by age, sex, and combined oral contraceptive use (which could be a confounder with respect

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to migraine outcomes). Incident migraines (G43.x), fibromyalgia (M79.7), multiple sclerosis (G35), and neuropathy (G62.0, G62.89, G62.9) were identified by ICD-10 codes. Cox proportional hazards regression was performed using Stata 17. Patients were followed until they experienced the outcome of interest or left the database. Given the use of de-identified data, this study was exempt from Institutional Review Board review.

Among 26,380 patients started on isotretinoin, who were matched with 26,380 patients started on a tetracycline-class antibiotic, 57.7% were female and the mean age was 25.3 (SD 8.8) (Table 1). Compared to those treated with tetracycline-class antibiotics, those treated with isotretinoin were not at increased risk of developing migraine (HR 0.91; 0.83–1.01), fibromyalgia (1.00; 0.98–1.01), multiple sclerosis (0.92; 0.43–1.96), or neuropathy (0.93; 0.66–1.32) (Table 2).

These results of this matched, retrospective cohort study highlight that isotretinoin is not associated with increased risk of migraine, fibromyalgia, multiple sclerosis, or neuropathy. While case series and registries such as the FDA Adverse Event Reporting System are an important source of risk signals in need of further study, these findings highlight the importance of cohort studies to assess whether there is additional evidence to support causality. This study is limited by its retrospective design; there is the potential for unmeasured confounding, though the use of matching decreases this risk. While further studies are warranted to examine whether these findings generalize to other populations, this study provides reassurance that isotretinoin use for acne is not associated with an increased risk of migraine, fibromyalgia, multiple sclerosis, or neuropathy.

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Table 1.

Cohort Characteristics

Characteristic	Isotretinoin (n=26,380)	Tetracyclines (n=26,380)
Age, y, mean (SD)	25.3 (8.8)	25.3 (8.8)
Age, y, median (IQR)	22 (19–28)	22 (19–28)
Female sex, n (%)	15,209 (57.7)	15,209 (57.7)
Oral contraceptive use *, n (%)	1900 (12.5)	1900 (12.5)
Continuous follow-up, d, mean (SD)	592.9 (397.2)	604.8 (398.66)

*among female patients

Table 2.

Risk of neurologic adverse events between those exposed to isotretinoin versus oral tetracycline-class antibiotics

Neurologic adverse event	Hazard Ratio; 95% CI
Migraine	0.91; 0.83–1.01
Fibromyalgia	1.00; 0.98–1.01
Multiple sclerosis	0.92; 0.43–1.96
Neuropathy	0.93; 0.66–1.32