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## Does treatment of acne with Retin A and tetracycline cause adverse effects?

### ■ EVIDENCE-BASED ANSWER

Adverse reactions to long-term tetracycline therapy are rare, and most will occur within 2 months of initiating therapy (strength of recommendation [SOR]: **B**, systematic review of ecological studies). Rare but serious drug reactions include a severe cutaneous reaction, hypersensitivity syndrome reaction, serum sickness–like reaction, and isolated single-organ dysfunction (SOR: **B**, systematic review).

Duration of antibiotic treatment is strongly associated with increased bacterial resistance (SOR: **B**, systematic review and 1 outcomes study), but antibiotics for acne do not appear to interfere with oral contraceptive efficacy (SOR: **B**, case-control study and supporting expert opinion). Laboratory monitoring is not indicated in otherwise healthy patients (SOR: **B**, consistent cohort studies).

No reports have been published regarding long-term topical tretinoin (Retin A) therapy. Short-term follow-up reports note no systemic effects (SOR: **C**, expert opinion), no teratogenicity (SOR: **B**, single case control study), and negligible systemic absorption (SOR: **B**, outcome studies).

Thus, long-term topical tretinoin is presumed to be safe (SOR: **C**, expert opinion and extrapolation of pharmacologic data).

### ■ EVIDENCE SUMMARY

#### Tetracycline

A study of the safety of tetracycline,<sup>1</sup> which used reports in a drug safety database and a literature review of reported adverse events, concluded that rare but serious events do occur with tetracycline. Severe cutaneous adverse reaction was the most common reported single-organ dysfunction. Other rare events included hypersensitivity syndrome reactions and serum sickness–like reactions.

Since baseline rates of tetracycline use are unknown, it is impossible to ascertain the event rates for these rare reactions. Most of these serious adverse events occur less than 2 months after initiating therapy; they typically include general symptoms such as fever, malaise, and arthralgias, but may also include major organ involvement. The study suggested no clear treatment for these complications, but recommended discontinuing tetracycline and avoiding the entire tetracycline class of drugs.<sup>1</sup> No evidence supports previous concerns that tetracycline causes drug-induced lupus.

A systematic review confirms that treating acne with long-term systemic antibiotics leads to increased antimicrobial resistance.<sup>2,3</sup> A well-designed cohort trial showed that *Propionibacterium acnes* resistance was directly related to duration of antibiotic therapy.<sup>4</sup> This is clinically important because resistance levels correlate with therapeutic failure.<sup>2</sup> Rotating antibiotics on a long-term basis actually increases bacterial resistance patterns and can exacerbate the problems of increasing resistance and poor treatment outcomes.<sup>2</sup>

A relatively large retrospective cohort study of oral contraceptive users in a dermatological practice showed no difference in contraceptive failure rates between those prescribed common antibiotics (including tetracycline) and controls (1.6% vs 0.96%; 95% confidence interval [CI] for the difference, 0.81–2.1).<sup>5</sup>

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TABLE 1

## Side effects of tetracycline and topical tretinoin

Tetracycline	Side-effect rates
Vaginal candidiasis <sup>8</sup>	12%
Gastrointestinal complaints <sup>8*</sup>	4%
Gram-negative folliculitis <sup>9</sup>	4%
Topical tretinoin <sup>10</sup>	Maximal observed side-effect rates
Peeling	50%
Burning	49%
Erythema	49%
Skin tightness	42%
Dryness	40%
Itching	24%

\* Gastrointestinal complaints included nausea, diarrhea, black hairy tongue, esophagitis, and flatulence.

A systematic review of 8 studies reported on 777 patients taking antibiotics for acne, and examined the need for laboratory monitoring of long-term tetracycline users, including renal, liver, and blood components. The authors found only 1 adverse drug reaction (mild hyperbilirubinemia). They concluded that routine lab monitoring for all patients on long-term antibiotics for acne rarely detects clinically concerning adverse drug reactions and would be cost-prohibitive.<sup>6</sup>

Minor adverse side effects of tetracycline therapy are reported in about 8% of patients.<sup>7</sup> Some of the relatively more common and benign side effects are summarized in **Table 1**.

### Topical tretinoin (Retin A)

Most published studies on topical tretinoin (Retin A) focus on the side effect of minor skin irritation. A multicenter, double-blind parallel study<sup>10</sup> compared the safety and efficacy of 2 formulations of tretinoin gel formulations. Adverse dermatologic side effects commonly reported are in **Table 1**.

These cutaneous irritant side effects, while noted in up to 50% of treated patients, peaked in 7 days and decreased significantly over time.

Topical tretinoin has been in clinical use for more than 25 years. Topical delivery results in a very low systemic exposure; plasma retinoid levels measured after topical use remain at or below endogenous levels, likely due to very limited absorption.<sup>11</sup> Topical tretinoin is not associated with an increased risk for major congenital disorders. A retrospective study of 215 women on tretinoin during the first trimester compared with 430 controls found that the relative risk for a major congenital anomaly was 0.7 (95% CI, 0.2–2.3). The authors concluded that topical tretinoin did not increase congenital anomaly risk.<sup>12</sup>

### RECOMMENDATIONS FROM OTHERS

No clinical guidelines have been published about the long-term use of tetracycline or topical tretinoin. An ad hoc committee of the American Academy of Dermatology concluded “tetracycline

TABLE 2

**Treatment recommendations to reduce antimicrobial resistance**

Do not prescribe systemic antibiotics if a topical medication will suffice

Avoid concomitant topical and systemic use of different antibiotics

Antibiotic therapy should continue for no longer than necessary, with a maximum period of 6 months

Do not "switch" or "rotate" antibiotics in patients who are not responding to therapy

Try systemic retinoids if acne fails to respond within 6 months of antibiotic therapy or quickly relapses

Adapted from Cooper et al.<sup>2</sup>

is a rational, effective, and relatively safe drug for use in the treatment of acne vulgaris when given in a dosage of 1 gm or less per day for long term therapy.<sup>77</sup> Other experts, more concerned with growing antibiotic resistance, recommend steps to help prevent increasing resistance (Table 2).

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**CLINICAL COMMENTARY****Use a judicious approach to topical agents and systemic antibiotics**

We should use a judicious approach with appropriate use of topical agents to treat acne. In those cases where acne is not responding, systemic antibiotics can be quite effective and very well tolerated. Regarding antimicrobial resistance of *P acnes*, we should avoid changing antibiotics unnecessarily, and taper to the lowest effective dose once the acne is well controlled. I think the dictum to avoid treating with systemic antibiotics for longer than 6 months is not widely followed. Often, much longer courses of treatment are necessary. For an individual patient, the risk of developing resistant *P acnes* is often preferable to the alternatives of inadequate acne control or systemic isotretinoin. Periodic attempts should be made to discontinue antibiotics when acne is well controlled, with resumption of the same antibiotic if one continues to be needed.

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