Potential harms of long-term acne treatment with oral antibiotics

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Clinical Inquiries question

What are the potential harms of long-term acne treatment with oral antibiotics?

Evidence-based answer

Specific evidence attributing adverse effects to long-term acne treatment with oral antibiotics is lacking. However, nausea, vomiting, or diarrhea are seen in 7% of patients taking tetracyclines, 4% taking macrolides, and 2% taking clindamycin. Tetracyclines also cause dizziness, headache, and photosensitivity in 2% of patients (strength of recommendation [SOR] A: based on meta-analyses of randomized controlled trials [RCTs]). In addition, tetracyclines are associated with rare hypersensitivity reactions (pneumonitis, eosinophilic nephritis, serum sickness) and intracranial hypertension (SOR C: based on case reports). Minocycline might increase the risk of systemic lupus erythematosus (SLE), autoimmune hepatitis, and polyarteritis nodosa, generally after 1 year of use (SOR B: based on retrospective cohort and case-control studies). Macrolides are associated with cardiac conduction abnormalities and, rarely, hepatotoxicity. Clindamycin is associated with pseudomembranous colitis (SOR C: based on case reports).

Evidence summary

Physicians most commonly select from 3 classes of medications (tetracyclines, macrolides, and clindamycin) when indicating oral antibiotics for the treatment of acne. The potential harms or adverse effects of this antibiotic use are described below.

Tetracyclines (tetracycline, oxytetracycline, lymecycline, doxycycline, minocycline). A 2012 systematic review of studies of adverse effects largely associated with minocycline divided the types of adverse effects into 3 categories: early dose-related effects on single organ systems (vestibular, gastrointestinal, dermatologic), hypersensitivity reactions (pneumonitis, eosinophilic nephritis, serum sickness), and autoimmune disorders (SLE, autoimmune hepatitis, polyarteritis nodosa).[1] While minocycline commonly produced adverse effects in single organ systems (332 of 1906 patients [17.4%] in 29 RCTs), it did not often result in discontinuation of the drug (79 of 2143 patients [3.7%] in 34 RCTs withdrew as a result of adverse effects), but there were more withdrawals due to adverse effects than with placebo (relative risk of 1.08; 95% CI 1.03 to 1.13). Furthermore, a 2006 systematic review of placebo-controlled RCTs of oral antibiotics for acne reported that tetracyclines produced mild gastrointestinal adverse effects in 7% of participants, dizziness and headache in 2%, and photosensitivity in 2%.[2] In the 2012 systematic review, the authors identified 56 cases of hypersensitivity disorders associated with tetracyclines over 40 years, and 3 cases of serum sickness.[1] They also found a retrospective cohort study and 3 case-control studies evaluating autoimmune disorders associated with minocycline, which showed increased risk of SLE (2.6 to 8.5 times) and liver dysfunction (2.1 times), particularly with use longer than 1 year (**Table 1**).[1] A systematic review of intracranial hypertension induced by acne medication–associated cases of pseudotumor cerebri (PTC) with tetracycline use, with symptoms manifesting in hours to months.[3] Doxycycline and minocycline were also associated with PTC, but those reported cases were few. Most cases of PTC induced by minocycline occurred in teenagers and young adults.

Macrolides (erythromycin, azithromycin). Two systematic reviews of antibiotic treatments for acne,[4,5] both predominantly involving teenagers and young adult populations, described gastrointestinal symptoms (nausea, vomiting, and abdominal pain) as the most common adverse effects of erythromycins (incidence of 4% with erythromycin stearate and 20% with erythromycin base[2]). A meta-analysis[5] of 6 RCTs (N = 906) comparing oral azithromycin and oral doxycycline for acne reported severe diarrhea necessitating discontinuation in 4 patients. One systematic review of 22 mostly open-label studies evaluating the efficacy of azithromycin in acne treatment found few gastrointestinal adverse effects and noted the absence of photosensitivity.[6] The authors of the 2 previously mentioned meta-analyses[3,4] also described cardiac conduction abnormality as a rare adverse effect, based on case reports (incidence specific to acne patients not supplied). A retrospective cohort study evaluating use of oral erythromycin in middle-aged adults found that it was associated with a higher risk of sudden cardiac death.[7] The authors reviewed 1 249 943 person-years of follow-up of oral erythromycin use in a Tennessee Medicaid population (average age 45 years; 25% of the cohort older than 65 years) and found 1.2 deaths per 1000 person-years (incidence rate ratio of 2.01; 95% CI 1.08 to 3.75). However, erythromycin use for acne was not specified. Patients concurrently taking cytochrome P450 3A inhibitors with oral erythromycin

Table 1. Possible adverse effects associated with acne treatment with oral tetracycline, oxytetracycline, minocycline, and erythromycin: *Statistically significant adverse effects are highlighted in bold.*

DRUG	ADVERSE EFFECT	STUDY TYPE	NO. OF PARTICIPANTS	RISK (95% CI)	COMMENTS
Minocycline	SLE	Retrospective cohort	97 694	• HR = 2.64 (1.51 to 4.66)	• Prevalence of 8.8 cases per 100 000 patient-years • Risk increases with long-term use
Minocycline	SLE	Case-control	875	• OR = 4.23 (1.03 to 42.74)	NA
Minocycline or other tetracyclines	SLE	Case-control	27 688	• **8.5 (2.1 to 3.5) for minocycline** • 1.7 (0.4 to 8.1) for other tetracyclines	Absolute risk for tetracyclines is 52.8 cases per 100 000 prescriptions
Minocycline, tetracycline or oxytetracycline, and erythromycin	Liver dysfunction	Case-control	29 332	• **ORadj = 2.10 (1.30 to 3.40) for minocycline** • ORadj = 1.46 (0.81 to 2.64) for tetracycline or oxytetracycline • ORadj = 1.64 (0.71 to 3.80) for erythromycin	Incidence was 1.04 cases per 10 000 exposed person-months with minocycline, and 0.69 cases per 10 000 exposed person-months with tetracycline or oxytetracycline

HR—hazard ratio, ORadj—adjusted odds ratio, NA—not applicable, OR—odds ratio, SLE—systemic lupus erythematosus.
Data from Garner et al.[1]

had a 5-fold increased risk of cardiac death.[7] Based on case reports, macrolides are rarely associated with hepatotoxicity (incidence not supplied).[8]

Clindamycin. The aforementioned systematic review found more mild diarrhea in a clindamycin group than the placebo group, though it was not significant. Additionally, pseudomembranous colitis occurred in 1 patient (N = 42).[2]

Recommendations from others

The 2016 American Academy of Dermatology guidelines for the treatment of acne recommended that systemic antibiotics for moderate to severe acne should be used for the shortest possible duration, with reevaluation at 3 to 4 months, in order to minimize antibiotic resistance.[8]

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Competing interests
None declared

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