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Safety of longer-term doxycycline use: A systematic review and meta-analysis with implications for bacterial STI chemoprophylaxis

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Abstract

Background: Sexually transmitted infections (STIs) such as syphilis, gonorrhea, and chlamydia have significantly increased over the past decade in the United States. Doxycycline as chemoprophylaxis (i.e., post-exposure prophylaxis [PEP]) offers promise for addressing bacterial STIs. The goal of the current study was to evaluate the safety of longer-term doxycycline use (defined as eight or more weeks) in the context of potential use as STI chemoprophylaxis through a systematic literature review and meta-analysis.

Methods: This review used the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to search MEDLINE/PubMed for clinical studies published from August 2003 through January 2023 that reported on adverse events with doxycycline use with a focus on side-effects and metabolic effects of long-term use.

Results: A total of 67 studies were included in the systematic review. Overall, studies on longer-term doxycycline use reported 0% to over 50% adverse events ranging from mild to severe. Most common adverse events included gastrointestinal symptoms (i.e., nausea, vomiting, and abdominal pain), dermatologic (i.e., rash), and neurological (i.e., headache and dizziness) symptoms. Discontinuation of doxycycline due to adverse events was relatively uncommon in most studies. A meta-analysis of placebo controlled clinical trials (N=18) revealed gastrointestinal and dermatological adverse events were more likely to occur in the doxycycline group.

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Conclusion: Longer-term (8+ weeks) doxycycline use is generally safe and may be associated with minor side-effects. Further research is needed on the potential metabolic impact of longer-term doxycycline use.

Short Summary:

A systematic review of longer-term doxycycline (8+ weeks) found the medication was generally well-tolerated and safe. Findings have implications for doxycycline as chemoprophylaxis for the prevention of sexually transmitted infections.

INTRODUCTION

Bacterial sexually transmitted infections (STIs) such as syphilis, gonorrhea, and chlamydia have significantly increased over the past decade in the United States (US) with approximately 2.5 million reported cases in 2021 (1). Importantly, cases of STIs disproportionately impact certain populations including gay, bisexual, and other men who have sex with men (MSM) and transgender women (TGW), as well as African American/Black and Hispanic/Latino communities. One potential approach to addressing the increasing burden of STIs includes chemoprophylaxis with antimicrobials and specifically doxycycline. Recent studies have evaluated doxycycline as post-exposure prophylaxis (PEP), taking the medication *after* a potential STI exposure, and found that this approach effectively reduces bacterial STIs in MSM and TGW (2–5). This novel approach offers a potentially powerful tool to address the increasing burden of bacterial STIs in the US.

Doxycycline was initially evaluated as pre-exposure prophylaxis (PrEP) to prevent bacterial STIs in a pilot study in 2015 which suggested potential benefits in a small cohort (N=30) of MSM with HIV when taken daily before an exposure occurred (5). Subsequent studies have evaluated doxycycline as PEP taken as a single 200mg dose ideally within 24 hours and up to 72 hours after condomless sex. The IPERGAY study conducted from July 2015 to January 2016 among MSM and TGW receiving HIV PrEP demonstrated efficacy of doxycycline as PEP in preventing syphilis and chlamydia but not gonorrhea (3). In 2022, the DoxyPEP study conducted in Seattle and San Francisco demonstrated that doxycycline as PEP prevented syphilis, gonorrhea and chlamydia in both MSM and TGW with HIV and those taking HIV PrEP (2). Other recent studies have confirmed that doxycycline is effective as PEP in preventing bacterial STIs in MSM and TGW (4). A single study found that doxycycline as PEP was not significant in cis-gender heterosexual women (6), which has been attributed to low adherence (7). Further studies of cis-gender women and other populations which also include doxycycline as PrEP for STI prevention are ongoing.

One important consideration for doxycycline as STI chemoprophylaxis is the safety of longer-term, intermittent use of the medication. Doxycycline was initially approved by the US Food and Drug Administration (FDA) in 1967. Doxycycline is generally well absorbed and tolerated, with a half-life of approximately 12 hours (8,9). The medication has been extensively used longer-term to treat acne and rosacea (10) and for prophylaxis to prevent scrub typhus (11), Lyme disease (12), tick-borne relapsing fever (13,14), leptospirosis (15–18), and malaria (19). Adverse effects most commonly associated with doxycycline hyclate have included photosensitivity (20) and esophageal erosion and ulceration (21). Adverse

effects generally resolve with discontinuation of the medication. However, despite the broad use of doxycycline, limited data is available on the longer-term safety of the medication.

A prior systematic review on the safety of doxycycline was published by Smith and Leyden, and reviewed data from 1966 to 2003 (22). The overall findings of this review included 24 clinical trials of doxycycline with a “very low” incidence of adverse events in general. Gastrointestinal adverse events were the most common side-effects reported. This review did not specifically focus on longer-term use and included a total of three studies with 20 days or longer use.

The goal of the current study was to evaluate the safety of longer-term doxycycline use (defined as eight or more weeks) in the context of potential use as STI chemoprophylaxis through a systematic literature review and meta-analysis.

METHODS

We used the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (23) to search MEDLINE/PubMed for clinical studies that reported on adverse events with doxycycline use with a focus on side-effects and metabolic effects of long-term use. The following search terms were used: “doxycycline” AND (“adverse reaction” OR “adverse event” OR “side effect”). The review was conducted for studies that were published from August 2003 through January 2023. We also included studies from a prior systematic review conducted for studies published from 1966 to August 2003 (22). Inclusion criteria for our initial screening included any retrospective or prospective clinical study with an average duration of two months (eight weeks) or more on doxycycline. Eight weeks or more was chosen given that people on doxycycline chemoprophylaxis would likely be taking the medication for months. There were no restrictions in regards to country; publication language; date; or patient age, race, gender, or sexuality. Exclusion criteria included: non-human subjects or in-vitro studies, unrelated papers, duplicates, unavailable full texts, abstract-only publications, and case reports. Papers that reported on doxycycline use in combination with other oral medications were generally excluded since it was difficult to identify the side effects from doxycycline alone. However, studies with multiple oral medications including doxycycline that evaluated metabolic effects were included given the overall paucity of data on this topic. After our initial screening, we also reviewed other review articles from the initial search to identify additional studies to include.

Each included article was manually reviewed for information about the study period, study type, and study population. We also collected information about the formulation, dose, and duration of doxycycline in each study. Articles were also reviewed for information about doxycycline adverse events, including severity of events (mild, moderate, severe) and type of clinical event (neurological, gastrointestinal, dermatological/skin, other). Severity of events was classified according to the definitions used by the study which reported the event. There was some variation, but in general, mild or moderate adverse events referred to those causing minimal or some interference with daily activities. Severe adverse events were those causing an inability to perform daily activities or those that were potentially life-threatening or resulted in hospitalization. For the clinical event type, we broadly included any specific

symptom of the clinic event type in the overarching group. For example, one study may have reported only nausea or diarrhea, and another included abdominal pain. All these various symptoms would be included under the gastrointestinal event type.

For the meta-analysis, we limited the included studies to only those reporting generally healthy individuals and reported adverse events for participants in both the doxycycline treatment arm and placebo groups. All statistical analyses and calculations of effect sizes were conducted in R using the Metafor statistical package (24). We calculated relative risk estimates and corresponding 95% confidence intervals (CIs) using a random-effects model to assess the rate of adverse events between the treatment group receiving doxycycline and a comparison group receiving placebo. We repeated all analyses using only studies that provided 100–200 mg dosages of doxycycline per day to reflect the dosage of doxycycline used as PEP to prevent STIs. Relative risk estimates were only calculated when three or more studies reported data for the outcome. Heterogeneity was assessed with the Q-test statistic and I^2 values, which describe the percentage of variation across studies that is attributable to heterogeneity rather than chance (25).

RESULTS

Systematic Review Results

We identified a total of N=828 total articles (Figure 1). After review, N=678 were excluded due to being unrelated and/or not clinical studies. The remaining 150 articles were manually assessed for eligibility. We excluded a total of 103 of these articles for the following reasons: doxycycline used for less than 8 weeks (n=61), non-clinical trial (n=17), doxycycline used in combination with other drugs (n=12), case report/case series (n=7), protocol description (n=3), non-oral doxycycline formulation used (n=1), commentary (n=1), and full text not available (n=1). The remaining 47 studies were included after this initial screening. We also manually reviewed an additional 28 review articles to determine if there were any relevant studies missed in our initial screening. This review led to 20 studies being identified and added to the initial screening, for a total of 67 studies included in our systematic review (Table 1). The 67 articles included in the review were published from 1987 to 2022. The most common studies include those focused on rosacea treatment (N=14), acne treatment (N=13), and malaria prophylaxis (N=11). One study specifically looked at doxycycline for STI PEP. Populations included those 9 years of age and older. Most studies were performed in the United States (N=21). Doxycycline doses ranged from 20mg to 200mg a day depending on the study. Time on doxycycline ranged from eight weeks (minimum study inclusion) to over three years. The total number of people in these studies who reported being on doxycycline was N=10,106 (Range: 7–1,196). Twenty-two studies report at least mild or moderate side-effects or adverse events related to doxycycline use ranging from 0% to 88%. Severe side-effects or adverse events in people on doxycycline ranged from 0% to 14% per study. These results should be interpreted in the setting of the specific study and patient population. For example, the study reporting 14% severe side-effects or adverse events was in the setting of doxycycline use in people with osteoarthritis and therefore potentially significant comorbidities (26). Although 14% of people reported severe side-effects or adverse events in the doxycycline group, the authors did mention that these

events were unlikely caused by doxycycline. Many studies that reported severe adverse events in individuals on doxycycline did not attribute the events to the medication (3,26–31). In the studies that did report severe adverse events for individuals on doxycycline, these included allergic reactions (27,30,32), dermatologic and skin reactions (33–35), gastrointestinal (32,34,35), and neurological (34–37).

In terms of specific side-effects and adverse events, studies varied on how they reported the data (i.e., number of individuals with an adverse event versus the total number of adverse events). Studies reporting neurological effects (i.e., headache and dizziness) ranged from 0% to 30+% of individuals. The study with the highest reported neurological side effects per individual (i.e., 33%) evaluated individuals taking doxycycline as malaria prophylaxis and included side-effects of headaches, dizziness, dreams, somnolence, insomnia, palpitations, and sexual dysfunction (38). In this study, the severity of adverse events was not reported, but no individuals stopped the medication due to an adverse event. Reports of gastrointestinal side effects and adverse events (i.e., nausea, vomiting, and abdominal pain) ranged from 0% to 50+%. The majority of gastrointestinal side-effects were noted to be minor. No studies specifically looked at Clostridium difficile infection. In the study with the highest reported gastrointestinal side effects per individual (i.e., 53%), individuals were taking doxycycline to minimize endometrial bleeding and reported high rates of nausea, vomiting and diarrhea (39). However, this was a smaller study (N=32 individuals) and no severe adverse events were reported. Dermatologic and skin reactions (i.e., rashes) ranged from 0% to 38% per individual and varied in terms of severity and symptoms. The study with the highest reported dermatologic side effects (i.e., 38%) was small (N=32 individuals) and reported acne as the major symptom with no reports of severe adverse events (39). A number of studies also reported other side effects such as vaginal candidiasis which was reported in a small number of individuals (28,30,39–43).

A total of eight studies mentioned evaluating at least one metabolic effect of doxycycline (i.e., weight, diabetes, cholesterol, and/or blood pressure) (26,28,31,44–48). No studies comprehensively evaluated doxycycline on metabolism. Findings ranged from no changes in weight and blood pressure (31,45,46) to significant weight gain (23%) (44) and/or elevated blood pressure (26,28,48) and hypercholesterolemia (47). These studies were descriptive in nature with limited sample sizes and lack of control groups.

In addition, few (N=6) studies focused on the effect of doxycycline on the microbiome (i.e., oral, respiratory, gut) ranging from no changes to significant impacts. These included three studies of the effect of doxycycline on the resistance profile of oral microflora bacteria (two with no resistance found, and one study with resistance) (36,49,50), two descriptive studies evaluating variations of bacterial flora in the gastrointestinal tract (44,51), and one study which found significant increases in bacterial resistance in the respiratory tract after doxycycline use (52). However, these studies were largely descriptive in nature and limited by sample size and lack of control groups.

Meta-analysis Results

From the 67 studies included in the review, we limited the meta-analysis to only placebo-controlled studies with complete data reported for both arms (N = 18). For each type of

adverse event, the number of studies included in the analysis varied. For example, eleven studies reported neurological adverse events while only nine studies reported dermatological adverse events (Table 2). There was a significant difference in experiencing gastrointestinal and dermatological adverse events between the treatment and placebo groups (Table 2).

Participants in the doxycycline treatment group had an increased risk of experiencing gastrointestinal [RR: 1.68 (95% CI: 1.19, 2.38); p-value < 0.01] and dermatological [RR: 3.55 (95% CI: 1.39, 9.01); p-value = 0.01] adverse events compared to participants in the placebo control group. Similarly, for studies that reported dosages of 100–200 mg of doxycycline, participants in the doxycycline group had and increased risk of experiencing gastrointestinal [RR: 1.78 (95% CI: 1.16, 2.74); p-value = 0.01] and dermatological [RR: 5.52 (95% CI: 1.75, 17.42); p-value < 0.01] adverse events compared to the placebo group (Figure 2). No significant differences were observed for any, severe, or neurological adverse events for all included studies and for studies that reported administering doses of 100–200 mg of doxycycline.

Finally, we observed differences in participants withdrawing from the trial between the groups. Participants were more likely to withdraw due to adverse events in the doxycycline group compared to the placebo group for all included studies and among studies that reported dosages of 100 – 200 mg; RR: 1.62 (95% CI: 1.12, 2.34); p-value = 0.01 and RR: 1.82 (95% CI: 1.06, 3.11); p-value = 0.03, respectively. Observed heterogeneity as measured by I^2 across all analyses was 1–82% with a median of 33%. In analysis of outcomes where heterogeneity was high (45–82%), one to two studies (outliers) could explain the between-study variance not from chance alone.

DISCUSSION

This is the most comprehensive systematic review to date of longer-term doxycycline use and risk of adverse events. Studies included in the review were diverse in terms of population and reason for doxycycline use. Evaluation of adverse events was also limited by lack of standardized reporting methods leading to different definitions and approaches to analyzing adverse events. Overall, studies on longer-term doxycycline use reported 0% to over 50% adverse events ranging from mild to severe. Most common adverse events included gastrointestinal (i.e., nausea, vomiting, and abdominal pain), dermatologic (i.e., rash), and neurological (i.e., headache and dizziness) symptoms. However, discontinuation of doxycycline due to adverse events was relatively uncommon in most studies, though more likely among those on doxycycline than those taking a placebo. The meta-analysis of placebo controlled clinical trials revealed an increased risk of individuals on doxycycline experiencing gastrointestinal or dermatological adverse events compared to placebo. In summary, adverse events related to longer-term doxycycline use are commonly reported, but serious side-effects are rare.

Although common side-effects of doxycycline have been well described, longer-term doxycycline use could have other effects including on the microbiome and/or metabolism. No comprehensive evaluation of longer-term doxycycline use has rigorously evaluated changes in the microbiome or metabolism. Longer-term use (i.e., 24 months) of lower dose

doxycycline (i.e., doses ranging from 10mg a day to 20mg twice a day) does not seem to lead to an effect on the composition of doxycycline resistant species of the intestinal or vaginal flora (53,54), or increase the risk of *C. difficile* infection (55). In the current review, metabolic outcomes were not routinely evaluated. Studies that did include aspects of metabolism did not rigorously or comprehensively evaluate outcomes. Further research is needed to identify longer-term impact of doxycycline use on metabolism.

In the context of chemoprophylaxis for bacterial STIs, the current study has several important implications. First, severe adverse events due to longer-term doxycycline use are uncommon which is reassuring. Second, further study is needed on other possible longer-term side-effects including adverse impacts on metabolism. Third, all the reviewed studies focused on daily doxycycline use. Current bacterial STI chemoprophylaxis studies have evaluated doxycycline use as PEP which would generally represent intermittent, not daily use. We would hypothesize that intermittent doxycycline use would lead to fewer side-effects in general, although how much less is unclear. Previous studies have and other studies are currently evaluating daily doxycycline use as PrEP. Doxycycline as PEP for bacterial STI prophylaxis may be ideal in in terms of balancing risk for adverse events as well as antimicrobial resistance concerns compared to daily use as PrEP though further investigation is warranted.

Available studies varied in terms of study population, dosing, comparator drugs, co-morbidities, and outcomes evaluated. Importantly, the measures used to evaluate adverse events were not standardized requiring us to reduce the number of studies included in the meta-analysis. The meta-analysis demonstrated an increased risk of individuals on doxycycline experiencing gastrointestinal or dermatological adverse events compared to placebo which is consistent with the systematic review and clinical experience. Lack of systematic approaches in evaluating adverse events led to further challenges. In addition, the current study did not evaluate adverse pregnancy outcomes related to doxycycline use. Despite these challenges, the current study provides important insights into the safety of longer-term doxycycline in the context of STI chemoprophylaxis.

In conclusion, a significant number of studies have evaluated longer-term (8+ weeks) doxycycline use. Mild to moderate side-effects are common including gastrointestinal, dermatologic and potentially neurological. More serious side-effects are less common but do occur. There is likely a dose dependent relationship on side-effects. Of note, almost all studies evaluated daily doxycycline use. It is unknown whether episodic use would lead to fewer side-effects or adverse events.

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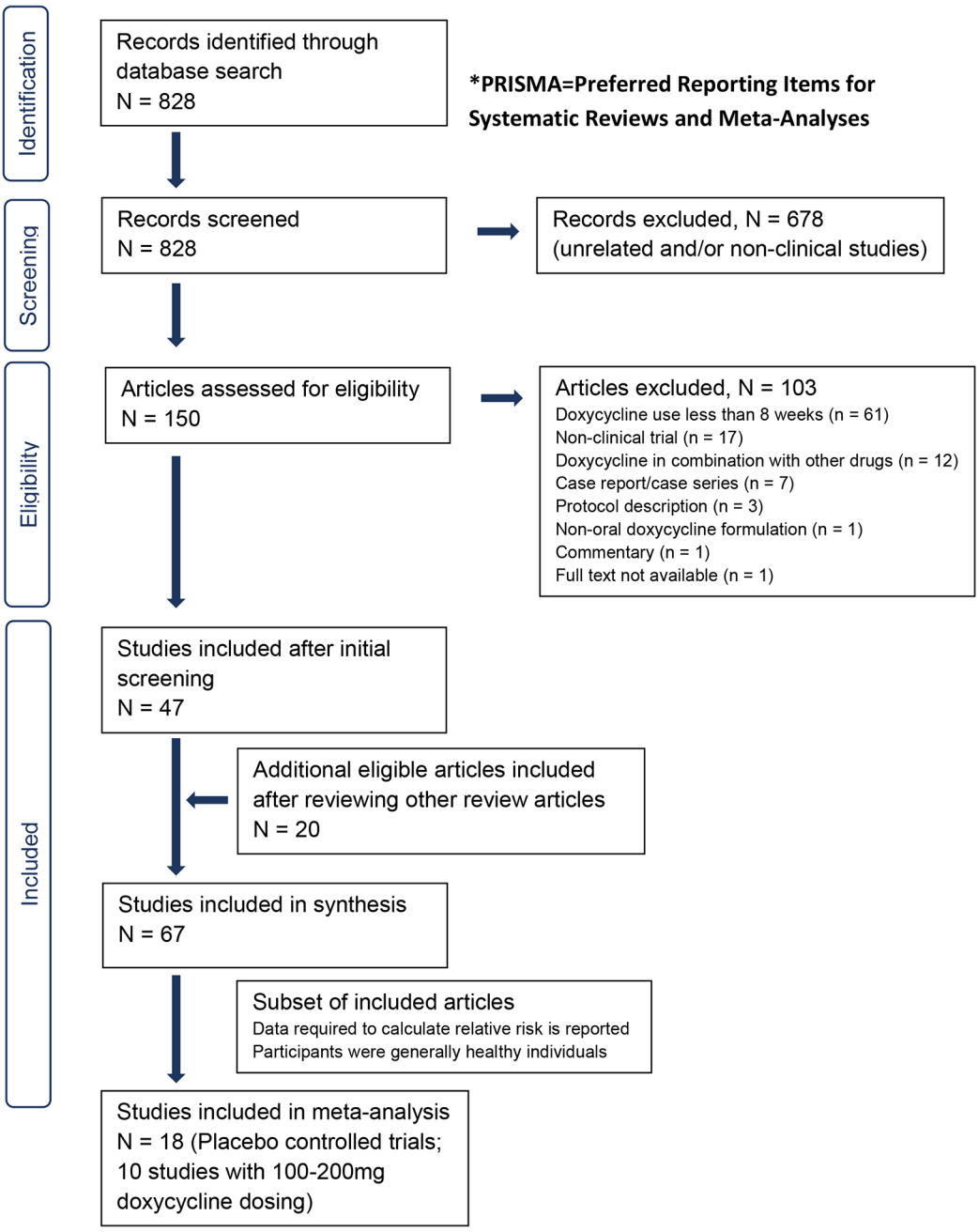
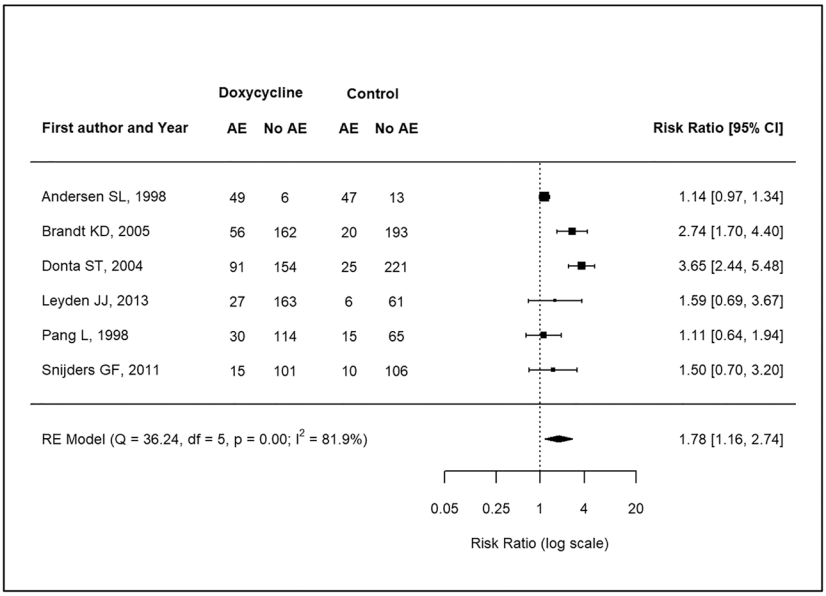


FIGURE 1:
PRISMA Diagram

Panel A:



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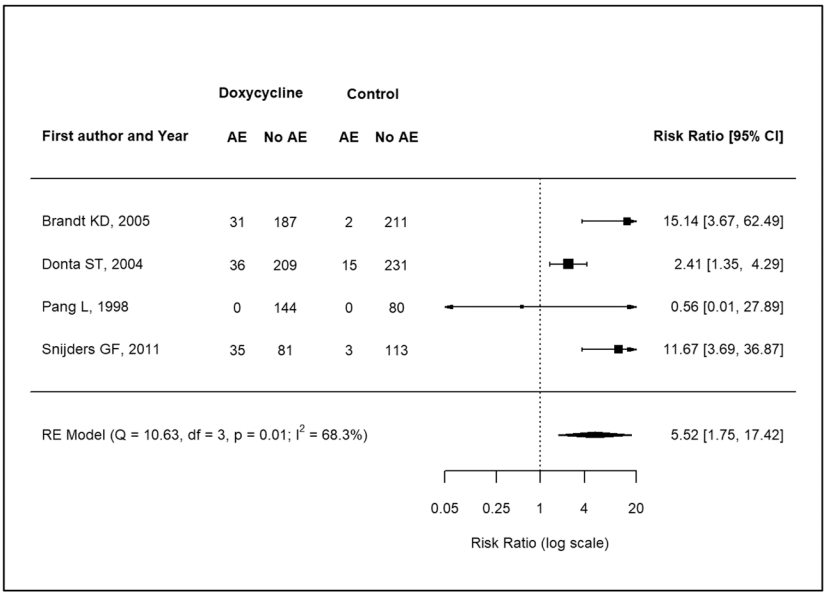

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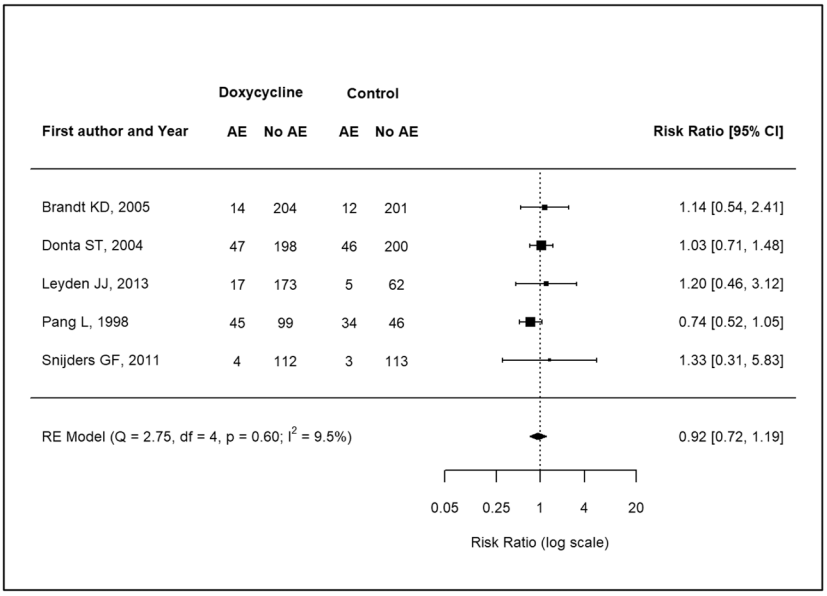

FIGURE 2:

Forest plots of (A) gastrointestinal, (B) dermatologic and (C) neurological adverse events among those taking 100–200mg of doxycycline daily compared to placebo.

*AE=Adverse Events, CI=Confidence Intervals, RE=Random Effects

TABLE 1:

Characteristics of studies identified by the systematic literature review that assess longer-term[1] doxycycline use and adverse events

First Author	Publication Year	Study	Population	Study Site	Drug	Duration (Days)	Doxycycline (N)	Mild * (n)	Moderate * (n)	Severe * (n)	Stopped (adverse events)
Akhyani (56)	2008	Rosacea Treatment	27–72 years old	Iran	Doxycycline 100mg once daily	91	30	NR	NR	NR	0
Alexis (57)	2012	Rosacea Treatment	18+ years old	United States	Doxycycline 40mg once daily (30 mg immediate release and 10 mg delayed release beads) once daily	84	1196	NR	NR	NR	NR
Andersen (58) **	1998	Malaria Prophylaxis	18–55 years old	Kenya	Doxycycline 100mg once daily	70	55	NR	NR	NR	1
Angelakis (44)	2014	Q Fever Endocarditis Treatment	18+ years old	France	Doxycycline 100mg twice a day (and hydroxychloroquine)	540+	48	NR	NR	NR	NR
Arman (59)	2015	Rosacea Treatment	Adults	Turkey	Doxycycline 100mg BID for one month then once daily for two months	90	19	NR	NR	NR	NR
Babaeinejad (60)	2011	Acne Treatment	13+ years old	Iran	Doxycycline 100mg once daily	90	50	4	0	0	0
Baudon (61)	1999	Malaria Prophylaxis	Adult soldiers	Gabon and the Central African Republic	Doxycycline 100mg once daily	120+	171	NR	NR	NR	11
Baxter (43)	2002	Abdominal Aortic Aneurysm Treatment	54–84 years old	United States (Multiple States)	Doxycycline 100mg twice per day	90+	36	NR	NR	NR	3
Berende (27)	2016	Lyme Disease Treatment	Adults	Netherlands	Doxycycline 100mg twice a day	84	86	39 (Mild or Moderate)	39 (Mild or Moderate)	3	3
Brandt (26) **	2005	Osteoarthritis Treatment	45–64 years old	United States (Indiana)	Doxycycline 100mg twice a day	900	218	NR	NR	31	25
Brill (52)	2015	COPD Treatment	45+ years old	United Kingdom	Doxycycline 100mg once daily	91	25	2 (Mild or Moderate)	2 (Mild or Moderate)	0	0
Caton (36) **	2000	Chronic Periodontitis	30–75 years old	United States (Multiple)	Doxycycline 20mg twice a day	274	93	NR	NR	1	1

Del Rosso (28) **	2007	Rosacea Treatment	18+ years old	United States and Puerto Rico	Doxycycline monohydrate 40mg once daily (formulation: 30-mg immediate-release and 10-mg delayed-release beads)	112	269	133 (Mild or Moderate)	133 (Mild or Moderate)	16	19
Del Rosso (62) **	2022	Acne Treatment	12+ years old	United States (Multiple Sites)	Doxycycline 120mg once daily (with trifarotene cream)	84	133	3 (Mild or Moderate)	3 (Mild or Moderate)	0	0
Del Rosso (63) **	2022	Rosacea Treatment	18–80 years old	United States (Multiple Sites)	Doxycycline 40mg modified-release capsules once daily	84+	300	12 (Mild or Moderate)	12 (Mild or Moderate)	0	0
Del Rosso (64)	2012	Rosacea Treatment	Adults	United States	Doxycycline modified-release 40mg once daily (30mg immediate-release and 10 mg delayed-release)	84	1196	NR	NR	NR	NR
Del Rosso (33)	2018	Acne Treatment	12+ years old	United States	Doxycycline hyclate delayed-release 100mg twice daily	84	175	26 (Mild or moderate)	26 (Mild or moderate)	1	4
Del Rosso (65)	2008	Rosacea Treatment	18+ years old	United States	Doxycycline 100mg daily or 40mg delayed-release daily (with topical metronidazole 1% gel)	112	91	16	18	6	9
Donta (29) **	2004	Gulf War Illness Treatment	Adult veterans	United States (Multiple sites)	Doxycycline 200mg once daily	365	245	NR	NR	12	7
Frenzel (30)	2008	Treatment of Brain Vascular Malformations	15–78 years old	United States (California)	Doxycycline 100mg twice a day	730	13	NR	NR	1	2
Gollnick (48)	2010	Rosacea Treatment	19–91 years old	Germany	Doxycycline 100mg once daily for 14 days then 50mg once daily	84	143	NR	NR	NR	NR
Golub (49)	2001	Chronic periodontitis treatment	18–75 years old	United States	Doxycycline 20mg once or twice daily	84	75	NR	NR	NR	3
Kaneshiro (39) **	2012	Prevention of Menstrual Bleeding	18–45 years old females	United States	Doxycycline 40mg once daily	84	32	NR	NR	NR	0
Kitchener (37)	2005	Malaria Prophylaxis	Adult soldiers	Australian soldiers	Doxycycline (Dose not reported)	180+	388	245 *	78 *	7 *	1

				settled in East Timor at risk for malaria							
Kus (66)	2005	Acne Treatment	18–30 years old	Turkey	Doxycycline 100mg BID for one month and then once daily for the next two months	90	26	NR	NR	NR	NR
Layton (20)	1993	Acne Treatment	13–49 years old	United Kingdom	Doxycycline 150 or 200 mg/day	183	106	NR	NR	NR	37
Lee (50) **	2004	Chronic periodontitis treatment	Adults	South Korea	Doxycycline hyclate 20mg twice daily	274	24	NR	NR	NR	NR
Leijtens (67)	2019	Suppression of Prosthetic Joint Infection	40–88 years old	Netherlands	Doxycycline 100–200mg once daily	1157	14	NR	NR	NR	1
Leyden (42) **	2013	Acne Treatment	12–45 years old	United States	Doxycycline calcium 40–160mg (weight based)	84	190	NR	NR	NR	1
Lin (45)	2015	Graves Disease Treatment	18–60 years old	China	Doxycycline 50mg once daily	84	16	2	0	0	0
Makunde (46)	2006	Wuchereria Bancrofti Treatment	14–68 years old	Tanzania	Doxycycline 200mg once daily	60	19	7	0	0	0
Maleszka (68)	2011	Acne Treatment	14+ years old	Poland and Croatia	Doxycycline 100mg once daily	84	120	NR	NR	NR	0
Molina (3)	2017	STI Prophylaxis	Adult Males	France	Single dose doxycycline 200mg within 24 hrs after sex and no later than 72 hrs	261+	116	102 (Mild or Moderate)	102 (Mild or Moderate)	4	8
Moore (32) **	2015	Acne Treatment	12–59 years old	United States	Doxycycline 40–100mg once daily	112	440	NR	NR	2	2
Naini (69)	2007	Diabetic Proteinuria Treatment	49–77 years old	Iran	Doxycycline 100mg once daily	61	35	NR	NR	0	3
Novak (70)	2002	Chronic periodontitis treatment	29–45 years old	United States	Doxycycline hyclate 20mg twice daily	183	10	NR	NR	NR	NR
Ohrt (38) **	1997	Malaria Prophylaxis	Adult soldiers	Indonesia	Doxycycline 100mg once daily	91	67	NR	NR	NR	0
Pagès (71)	2002	Malaria Prophylaxis	Adult soldiers	French soldiers deployed in Gabon and Chad	Doxycycline monohydrate 100mg once daily	120	275	NR	NR	NR	15
Pan (72) **	2022	Thyroid Disease	Adults	China	Doxycycline 50mg once daily	84	50	1	0	0	0

Pang (73) **	1998	Malaria Prophylaxis	10–16 years old	Thailand	Doxycycline 25–100mg daily depending on weight	105	144	NR	NR	NR	0
Pang (74)	1987	Malaria Prophylaxis	10–15 years old	Thailand	Doxycycline 100mg once daily for those over 40kg; Doxycycline 50mg once daily for those less than 40kg	63	95	NR	0	0	0
Parish (75)	2005	Acne Treatment	14–36 years old	United States	Doxycycline hyclate 100mg twice a day	56	12	NR	NR	NR	NR
Park (76)	2015	Rosacea Treatment	18+ years old	South Korea	Doxycycline 100mg twice a day	770	15	NR	NR	NR	0
Pfeffer (77)	2011	Rosacea Treatment	Adults	Germany	Doxycycline 40mg once daily (slow-release form)	60+	7	0	0	0	0
Pimenta (78)	2011	Lymphangioleiomyomatosis Treatment	Adult Females	Brazil	Doxycycline 100mg once daily	180	41	NR	NR	NR	0
Pimenta (79)	2013	Lymphangioleiomyomatosis Treatment	Adults	Brazil	Doxycycline 100mg once daily	365	41	NR	NR	NR	3
Popa (51)	2022	Colorectal Cancer Treatment	Adults	Romania	Doxycycline (Dose not reported)	56	10	NR	NR	NR	NR
Pradier (80)	2017	Suppression of Prosthetic Joint Infection	Adults	France	Doxycycline 200mg once daily	508+	39	NR	NR	NR	3
Pradier (81)	2018	Suppression of Prosthetic Joint Infection	18–91 years old	France	Doxycycline 200mg once daily	668	72	NR	NR	NR	6
Preshaw (31) **	2008	Chronic periodontitis treatment	24–81 years old	United States	Doxycycline monohydrate 40mg once daily (modified release)	274	133	79 (Mild or Moderate)	79 (Mild or Moderate)	9	7
Putschky (82)	2006	Reactive Arthritis Treatment	18–65 years old	Germany	Doxycycline 100mg twice a day	122	15	NR	NR	NR	0
Quarterman (83)	1997	Rosacea Treatment	31–66 years old	Georgia	Doxycycline 100mg once daily	84	39	NR	NR	NR	NR
Sanchez (84) **	2005	Rosacea Treatment	18+ year old females	United States and Puerto Rico	Doxycycline hyclate 20mg twice daily for 12 weeks (with metronidazole 0.75% topical lotion) followed by 4 weeks of monotherapy with doxycycline hyclate 20mg	112	20	NR	NR	0	0

Schlagenhauf (34)	2003	Malaria Prophylaxis	18–70 years old	Travel clinics in Switzerland, Germany, and Israel	Doxycycline monohydrate 100mg once daily	66	153	128	51	9	5
Sehgal (85)	2000	Leptospirosis prophylaxis	10+ years old	India	Doxycycline 200mg/ week	84	386	NR	NR	NR	3
Smith (35)	2011	Rheumatoid Arthritis Treatment	Adults	United States	Doxycycline 200mg once daily	90	484	31	53	26	35
Snijders (86) **	2011	Knee Osteoarthritis Treatment	Adults	Netherlands	Doxycycline monohydrate 100mg twice a day	168	116	NR	NR	NR	19
Sonmez (87)	2005	Malaria Prophylaxis	Adult soldiers	Turkish soldiers in Kabul, Afghanistan	Doxycycline 100mg once daily	84	506	395	32	0	NR
Tan (47)	2014	Acne Treatment	12–35 years old	Canada	Doxycycline hyclate 200mg once daily (with adapalene 0.1%/ benzoyl peroxide 2.5% gel)	140	133	NR	NR	0	6
Taylor (88) **	1999	Malaria Prophylaxis	18–55 years old	Indonesia	Doxycycline 100mg once daily	140	75	NR	NR	NR	1
Taylor (89)	2005	Wuchereria Bancrofti Treatment	15–68 year old males	Tanzania	Doxycycline 200mg once daily	56	34	8	NR	NR	0
Thiboutot (90)	2005	Acne Treatment	12–36 years old	United States (Multiple sites)	Doxycycline 100mg once daily	84	467	NR	NR	0	5
Thiboutot (40)	2009	Rosacea Treatment	19–83 years old	United States	Doxycycline monohydrate 100mg twice daily (with topical azelaic acid 15% gel)	28–84	172	19	8	4	12
Ullah (91)	2014	Acne Treatment	14–30 years old	Pakistan	Doxycycline 100mg once daily	90	193	NR	NR	NR	0
Ullah (92)	2022	Acne Treatment	12–24 years old	Pakistan	Doxycycline 100mg once daily	84	37	NR	NR	NR	NR
van der Linden (41)	2016	Rosacea Treatment	18+ years old	Netherlands	Doxycycline 40mg once daily	112	40	23 (Mild or Moderate)	23 (Mild or Moderate)	0	3
Weiss (93)	1995	Malaria Prophylaxis	9–14 years old	Kenya	Doxycycline 50mg once daily	77	32	NR	NR	NR	2

NR=Not reported

[1] Longer term was defined as 8+ weeks

[*] Events (not individuals)

[**] Included in the meta-analysis (N=18)

TABLE 2:

Relative risk of adverse events between doxycycline and placebo arms of randomized controlled trials

Outcome	κ	Relative risk (95% CI)	I^2%	P-value
Included RCT studies				
Any AE	9	1.03 (0.89, 1.21)	59.6	0.66
Severe AE	12	0.83 (0.59, 1.16)	2.20	0.28
Neurological AE	11	0.88 (0.73, 1.05)	0.90	0.15
Gastrointestinal AE	12	1.68 (1.19, 2.38)	72.2	<0.01
Dermatological AE	9	3.55 (1.39, 9.01)	45.9	0.01
Dropped due to AE	18	1.62 (1.12, 2.34)	7.50	0.01
100 – 200 mg dosages				
Any AE	3	1.35 (0.69, 2.64)	74.7	0.38
Severe AE	6	0.94 (0.65, 1.34)	0.00	0.73
Neurological AE	5	0.99 (0.97, 1.02)	0.17	0.68
Gastrointestinal AE	6	1.78 (1.16, 2.74)	81.9	0.01
Dermatological AE	4	5.52 (1.75, 17.42)	68.3	<0.01
Dropped due to AE	10	1.82 (1.06, 3.11)	20.9	0.03

κ = number of studies; AE = adverse event; I^2 variation across studies because of heterogeneity rather than chance; CI = confidence interval; RCT = randomized controlled trial