

# Doxycycline Use and Adverse Events

## Doxycycline use and adverse events search strategy:

MEDLINE/PubMed was searched for clinical studies that reported on adverse events with doxycycline use, specifically focusing on side-effects and metabolic effects of long-term use. Search terms included “doxycycline” AND (“adverse reaction” OR “adverse event” OR “side effect”). Some studies prior to 2003 were included but the systematic review was focused on studies published subsequent to a prior systematic review published by Smith and Leyden (Smith K, Leyden JJ. Safety of doxycycline and minocycline: a systematic review. Clin Ther. 2005 Sep;27(9):1329-42.).

Inclusion criteria for initial screening included any retrospective or prospective clinical study with an average duration of 2 months (8 weeks) or more on doxycycline. No restrictions set regarding 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 papers, case reports and any papers that reported on doxycycline use in combination with other drugs since it would not be possible to identify side effects from doxycycline alone. After the initial screening, review articles from the initial search were reviewed to identify additional studies to include.

## Characteristics of studies identified by the systematic literature review that assess longer-term1 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 (27)	2008	Rosacea Treatment	27-72 years old	Iran	Doxycycline 100mg once daily	91	30	NR	NR	NR	0
Alexis (28)	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 (29)**	1998	Malaria Prophylaxis	18-55 years old	Kenya	Doxycycline 100mg once daily	70	55	NR	NR	NR	1
Angelakis (30)	2014	Q Fever Endocarditis Treatment	18+ years old	France	Doxycycline 100mg twice a day (and hydroxychloroquine)	540+	48	NR	NR	NR	NR
Arman (31)	2015	Rosacea Treatment	Adults	Turkey	Doxycycline 100mg BID for one month then once daily for two months	90	19	NR	NR	NR	NR
Babaeinejad (32)	2011	Acne Treatment	13+ years old	Iran	Doxycycline 100mg once daily	90	50	4	0	0	0
Baudon (33)	1999	Malaria Prophylaxis	Adult soldiers	Gabon and the Central African Republic	Doxycycline 100mg once daily	120+	171	NR	NR	NR	11
Baxter (34)	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 (35)	2016	Lyme Disease Treatment	Adults	Netherlands	Doxycycline 100mg twice a day	84	86	39 (Mild or Moderate)	39 (Mild or Moderate)	3	3
Brandt (36)**	2005	Osteoarthritis Treatment	45-64 years old	United States (Indiana)	Doxycycline 100mg twice a day	900	218	NR	NR	31	25

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Brill (37)	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 (38)**	2000	Chronic Periodontitis	30-75 years old	United States (Multiple)	Doxycycline 20mg twice a day	274	93	NR	NR	1	1
Del Rosso (39)**	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 (40)**	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 (41)**	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 (42)	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 (43)	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 (44)	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 (45)**	2004	Gulf War Illness Treatment	Adult veterans	United States (Multiple sites)	Doxycycline 200mg once daily	365	245	NR	NR	12	7
Frenzel (46)	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 (47)	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 (48)	2001	Chronic periodontitis treatment	18-75 years old	United States	Doxycycline 20mg once or twice daily	84	75	NR	NR	NR	3
Kaneshiro (49)**	2012	Prevention of Menstrual Bleeding	18-45 years old females	United States	Doxycycline 40mg once daily	84	32	NR	NR	NR	0
Kitchener (50)	2005	Malaria Prophylaxis	Adult soldiers	Australian soldiers settled in East Timor at risk for malaria	Doxycycline (Dose not reported)	180+	388	245*	78*	7*	1
Kus (51)	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 (18)	1993	Acne Treatment	13-49 years old	United Kingdom	Doxycycline 150 or 200 mg/day	183	106	NR	NR	NR	37
Lee (52)**	2004	Chronic periodontitis treatment	Adults	South Korea	Doxycycline hyclate 20mg twice daily	274	24	NR	NR	NR	NR

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Leijtens (53)	2019	Suppression of Prosthetic Joint Infection	40-88 years old	Netherlands	Doxycycline 100-200mg once daily	1157	14	NR	NR	NR	1
Leyden (54)**	2013	Acne Treatment	12-45 years old	United States	Doxycycline calcium 40-160mg (weight based)	84	190	NR	NR	NR	1
Lin (55)	2015	Graves Disease Treatment	18-60 years old	China	Doxycycline 50mg once daily	84	16	2	0	0	0
Makunde (56)	2006	Wuchereria Bancrofti Treatment	14-68 years old	Tanzania	Doxycycline 200mg once daily	60	19	7	0	0	0
Maleszka (57)	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 then 72 hrs	261+	116	102 (Mild or Moderate)	102 (Mild or Moderate)	4	8
Moore (58)**	2015	Acne Treatment	12-59 years old	United States	Doxycycline 40-100mg once daily	112	440	NR	NR	2	2
Naini (59)	2007	Diabetic Proteinuria Treatment	49-77 years old	Iran	Doxycycline 100mg once daily	61	35	NR	NR	0	3
Novak (60)	2002	Chronic periodontitis treatment	29-45 years old	United States	Doxycycline hyclate 20mg twice daily	183	10	NR	NR	NR	NR
Ohrt (61)**	1997	Malaria Prophylaxis	Adult soldiers	Indonesia	Doxycycline 100mg once daily	91	67	NR	NR	NR	0
Pagès (62)	2002	Malaria Prophylaxis	Adult soldiers	French soldiers deployed in Gabon and Chad	Doxycycline monohydrate 100mg once daily	120	275	NR	NR	NR	15
Pan (63)**	2022	Thyroid Disease	Adults	China	Doxycycline 50mg once daily	84	50	1	0	0	0
Pang (64)**	1998	Malaria Prophylaxis	10-16 years old	Thailand	Doxycycline 25-100mg daily depending on weight	105	144	NR	NR	NR	0
Pang (65)	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 (66)	2005	Acne Treatment	14-36 years old	United States	Doxycycline hyclate 100mg twice a day	56	12	NR	NR	NR	NR
Park (67)	2015	Rosacea Treatment	18+ years old	South Korea	Doxycycline 100mg twice a day	770	15	NR	NR	NR	0
Pfeffer (68)	2011	Rosacea Treatment	Adults	Germany	Doxycycline 40mg once daily (slow-release form)	60+	7	0	0	0	0
Pimenta (69)	2011	Lymphangioliomyomatosis Treatment	Adult Females	Brazil	Doxycycline 100mg once daily	180	41	NR	NR	NR	0
Pimenta (70)	2013	Lymphangioliomyomatosis Treatment	Adults	Brazil	Doxycycline 100mg once daily	365	41	NR	NR	NR	3
Popa (71)	2022	Colorectal Cancer Treatment	Adults	Romania	Doxycycline (Dose not reported)	56	10	NR	NR	NR	NR
Pradier (72)	2017	Suppression of Prosthetic Joint Infection	Adults	France	Doxycycline 200mg once daily	508+	39	NR	NR	NR	3
Pradier (73)	2018	Suppression of Prosthetic Joint Infection	18-91 years old	France	Doxycycline 200mg once daily	668	72	NR	NR	NR	6

First Author	Publication Year	Study	Population	Study Site	Drug	Duration (Days)	Doxycycline (N)	Mild* (n)	Moderate* (n)	Severe* (n)	Stopped (adverse events)
Preshaw (74)**	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 (75)	2006	Reactive Arthritis Treatment	18-65 years old	Germany	Doxycycline 100mg twice a day	122	15	NR	NR	NR	0
Quarterman (76)	1997	Rosacea Treatment	31-66 years old	Georgia	Doxycycline 100mg once daily	84	39	NR	NR	NR	NR
Sanchez (77)**	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 (78)	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 (79)	2000	Leptospirosis prophylaxis	10+ years old	India	Doxycycline 200mg/week	84	386	NR	NR	NR	3
Smith (80)	2011	Rheumatoid Arthritis Treatment	Adults	United States	Doxycycline 200mg once daily	90	484	31	53	26	35
Snijders (81)**	2011	Knee Osteoarthritis Treatment	Adults	Netherlands	Doxycycline monohydrate 100mg twice a day	168	116	NR	NR	NR	19
Sonmez (82)	2005	Malaria Prophylaxis	Adult soldiers	Turkish soldiers in Kabul, Afghanistan	Doxycycline 100mg once daily	84	506	395	32	0	NR
Tan (83)	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 (84)**	1999	Malaria Prophylaxis	18-55 years old	Indonesia	Doxycycline 100mg once daily	140	75	NR	NR	NR	1
Taylor (85)	2005	Wuchereria Bancrofti Treatment	15-68 year old males	Tanzania	Doxycycline 200mg once daily	56	34	8	NR	NR	0
Thiboutot (86)	2005	Acne Treatment	12-36 years old	United States (Multiple sites)	Doxycycline 100mg once daily	84	467	NR	NR	0	5
Thiboutot (87)	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 (88)	2014	Acne Treatment	14-30 years old	Pakistan	Doxycycline 100mg once daily	90	193	NR	NR	NR	0
Ullah (89)	2022	Acne Treatment	12-24 years old	Pakistan	Doxycycline 100mg once daily	84	37	NR	NR	NR	NR
van der Linden (90)	2016	Rosacea Treatment	18+ years old	Netherlands	Doxycycline 40mg once daily	112	40	23 (Mild or Moderate)	23 (Mild or Moderate)	0	3
Weiss (91)	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)

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