

Review Article

Human demodicidosis and the current treatment options

人類蠕形蟎病和目前的治療方案

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Demodex folliculorum and *D. brevis* live and reproduce in the pilosebaceous unit, including hair follicles and sebaceous glands. Various treatments have been found to be effective in managing *Demodex*-related diseases. The possible effects of the treatments are to decrease the mite counts, relieve the related symptoms, and to modulate the immune system. Metronidazole, ivermectin, and permethrin are effective drugs for treating *Demodex* infections. A combination of different treatments is needed occasionally for refractory cases, especially those with genetic susceptibility or immuno-compromised conditions. Although the current treatments are effective in controlling *Demodex* mite population and the related symptoms, more investigations are needed to enhance efficacy by improved drug delivery technologies and alternative treatments with less toxicity, a lower risk of resistance, and better side-effects profile. This review summarises the current oral and topical treatments on human demodicidosis, their possible mechanisms of action, and side effects.

毛囊蠕形蟎和脂蠕形蟎在毛囊皮脂腺單位包括毛囊和皮脂腺中生活和繁殖。現有的各種治療在控制與蠕形蟎有關的疾病方面皆有成效。治療的效果可能是通過減少蟎蟲數量、緩解相關症狀或調節免疫系統。甲硝唑、伊維菌素和氯菊酯是治療蠕形蟎感染的有效藥物。偶爾需要結合應用不同的治療方案來治療難治的病例，尤其是那些具有潛在遺傳易感性或免疫功能受損的患者。儘管目前的治療方法在控制蠕形蟎數量及相關症狀方面是有效的，但仍需要進行更多的調查，改善藥物輸送技術以及採用毒性低、抗藥風險小和副作用輕的替代治療。本綜述總結了目前口服和局部用藥治療人蠕形蟎病的方案及其可能的作用機制和副作用。

Keywords: Crotamiton, demodicidosis, ivermectin, lindane, metronidazole, permethrin

關鍵詞：丁烯醯苯胺、蠕形蟎病、伊維菌素、林丹、甲硝唑、氯菊酯

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Introduction

Demodex spp. are mites from the subclass Acariformes of the class Arachnida. There are two species of *Demodex* in humans, *Demodex follicularium* and *Demodex brevis*, which are found in human pilosebaceous follicles and cause human demodicidosis, a transmittable parasitic dermatosis. The life cycle of *Demodex* mites is approximately 14-18 days from the egg to the larval stage and eventually the adult stage. The mating of the parasite takes place in the follicle opening and eggs are laid inside the hair follicles or sebaceous glands. *Demodex* mites are opportunistic pathogens and can be found on the skin or eyelashes of asymptomatic individuals. *Demodex*-related diseases occur when the host cutaneous environment facilitates their proliferation.¹

The pathogenesis of demodicidosis involves direct damage, blockage of the meibomian glands, and damage to the skin barrier of the follicles by the mite's claws and mouthpiece. Enzymes such as protease and lipase secreted by *Demodex* mites may stimulate host protease-activated receptors, promote the secretion of anti-microbial peptides, and upregulation of pro-inflammatory cytokines. Due to the adaptive immune response, CD4⁺ T helper cells infiltrate the site with other immune cells including macrophages and Langerhans cells. Patients with phenotypes HLA-Cw2 and HLA-Cw4 are more susceptible to *Demodex* overproliferation due to decrease in natural killer type-2 cells and Th1 cells adaptive immune response, whereas those with the HLA-A2 phenotype were less susceptible.² The chitin exoskeleton, crystalline waste products, and bacteria inside the mites such as *Streptococci*, *Staphylococci*, and *Bacillus oleronius* can trigger the inflammation cascade by the toll-like receptor (TLR)2 innate immunity pathway. The carbohydrate like Tn antigen expressed by *Demodex* can modulate the secretion of pro-inflammatory mediators such as interleukin (IL)-8 and tumour necrosis factor (TNF)- α from the pilosebaceous

unit of the host, which interferes with the innate immune response of the host to facilitate the invasion and population expansion of *Demodex*.³ Dermatological conditions associated with *Demodex* infections include acne vulgaris, pityriasis folliculorum, rosacea, perioral dermatitis, neutrophilic sebaceous adenitis, sebaceous adenoma, seborrhoeic dermatitis, papulo-pustular eruption, scalp folliculitis, and nipple infections.

Treatment of human demodicidosis

There are several classes of treatment for human demodicidosis, including systemic and topical therapies. Currently, metronidazole, ivermectin, doxycycline, permethrin, crotamiton, lindane (gamma hexachlorocyclohexane), benzyl benzoate, and pilocarpine are proven to have anti-*Demodex* effects. The current available drugs for human demodicidosis are summarised in Table 1 and the structures of these drugs are shown in Figure 1. However, none of them are 100% effective against *Demodex* mites and patient compliance due to complicated dosing regimens, repeated medication application, and side-effects are potential problems.

Metronidazole

Metronidazole is a small and highly-lipophilic synthetic nitroimidazole derivative, which is active against parasitic and anaerobic bacterial infections. Its mode of action in *Demodex*-associated rosacea is related to both the anti-inflammatory and anti-oxidant properties of the drug.⁴ Metronidazole can reduce the mite count,⁴ and relieve the dermatological signs and symptoms.⁵ It interferes with neutrophil release of reactive oxygen species (ROS) and inactivates existing ROS, which decreases the release of pro-inflammatory cytokines. Adverse effects include metallic taste in the mouth, nausea, vomiting, a disulfiram-like reaction with ingestion of alcohol, and the central nervous system (CNS) effects including seizures, encephalopathy, and ataxia.

Table 1. Currently available treatments for demodicidosis

Drug	Administration route	Action	Dosage	Side-effect	Reference
Metronidazole	Topical, oral	Reduce mite count, relieve dermatological symptoms, and have anti-inflammatory and anti-oxidant effects	Topical: 0.75-2% q.d. or b.i.d for 3-270 days Oral: 250 mg t.i.d. for 1-8 weeks	Topical: skin irritation, allergic dermatitis, aggravation of rosacea, erythema, pruritus, and flushing Oral: nausea, vomiting, headache, disulfiram-like reaction, and bitter metallic taste	(9,36)
Ivermectin	Topical, oral	Reduce mite count, relieve dermatological symptoms, and have immunomodulation effects	Topical: 1% q.d. for 2-12 weeks Oral: 200-250 µg/kg 2 doses 1-2 weeks apart	Topical: mild skin irritation, hypersensitivity, and mild and transient desquamation Oral: mild and transient desquamation, diarrhoea, nausea, headache, dizziness, fever, and oedema	(9)
Permethrin	Topical	Reduce mite count, relieve dermatological symptoms, and improve the erythema score	1-5% q.d. or b.i.d. for 3-12 weeks	Headache, dizziness, muscle spasms, convulsions, dystonic action of the neck, pruritus, and erythema	(37, 38)
Crotamiton	Topical	Reduce mite count, relieve dermatological symptoms, and have anti-pruritic effect	10% q.d. or b.i.d. for 3-45 days	Erythema, irritation, conjunctivitis, and contact dermatitis	(15, 39)
Lindane	Topical	Reduce mite count and relieve dermatological symptoms	1% q.d. for 10-15 days	Insomnia, irritability, vertigo, convulsions, restlessness, collapse, irritation, and allergic contact dermatitis	(15)
Doxycycline	Oral	Does not affect mite counts but can relieve inflammation associated with demodicidosis	40 or 50 mg q.d.	Oesophageal erosion, nausea, photosensitivity, photo-onycholysis, rash, diarrhoea, intracranial hypertension, hypoglycaemia, and anosmia	(40, 41)
Benzyl benzoate	Topical	Reduce mite count and relieve dermatological symptoms	10-25% b.i.d. for 45 days	Local irritation and severe burning sensation	(15)
Pilocarpine	Topical	Reduce mite count and relieve dermatological symptoms	4% q.d. for 2 weeks	N/A	(28)

b.i.d.: two times a day; q.d.: once a day; t.i.d.: three times a day

Metronidazole is safe in pregnancy, breastfeeding, and young infants, although it has carcinogenic potential. In some cases of *Demodex*-induced scalp folliculitis, oral metronidazole was unsuccessful in eradicating the mites.

Ivermectin

Ivermectin is derived from a group of naturally occurring macrocyclic lactones, called avermectins, extracted from the soil bacterium *Streptomyces avermectinius*, and may be used both topically and systemically. In addition to its well-known anti-*Onchocerca* and anti-filarial effects, ivermectin also has activities against other parasitic infections such as human demodicidosis. The anti-demodicidosis effect of ivermectin is probably due to its anti-parasitic, anti-inflammatory, and immunomodulatory properties. It can reduce the mite count⁶ and relieve *Demodex*-related dermatological signs and symptoms.⁷ The anti-parasitic activity of ivermectin is possibly due to its binding selectively to

glutamate or γ -aminobutyric acid (GABA) in the peripheral motor synapses of neurons, resulting in permanent opening of chloride ion channels, which inhibits the neuronal and muscular activities in the parasite and causes subsequent paralysis and death of the parasite. The anti-inflammatory properties of ivermectin are likely due to the inhibition of phosphorylation of the mitogen-activated protein kinases, JNK, and p38 as well as blocking the translocation of the transcription factor NF- κ B, which may decrease neutrophil phagocytosis and chemotaxis, inhibit pro-inflammatory cytokines such as IL-1 β , IL-8, and TNF- α , and upregulate the anti-inflammatory cytokine IL-10. The immune responses triggered by exogenous antigens are reported to be enhanced by ivermectin in animal studies.⁸ Compared to metronidazole, topical ivermectin treatment has a greater ability to reduce inflammatory lesions, with a fast onset of action. Adverse effects in topical ivermectin treatment are mostly mild, including skin irritation and

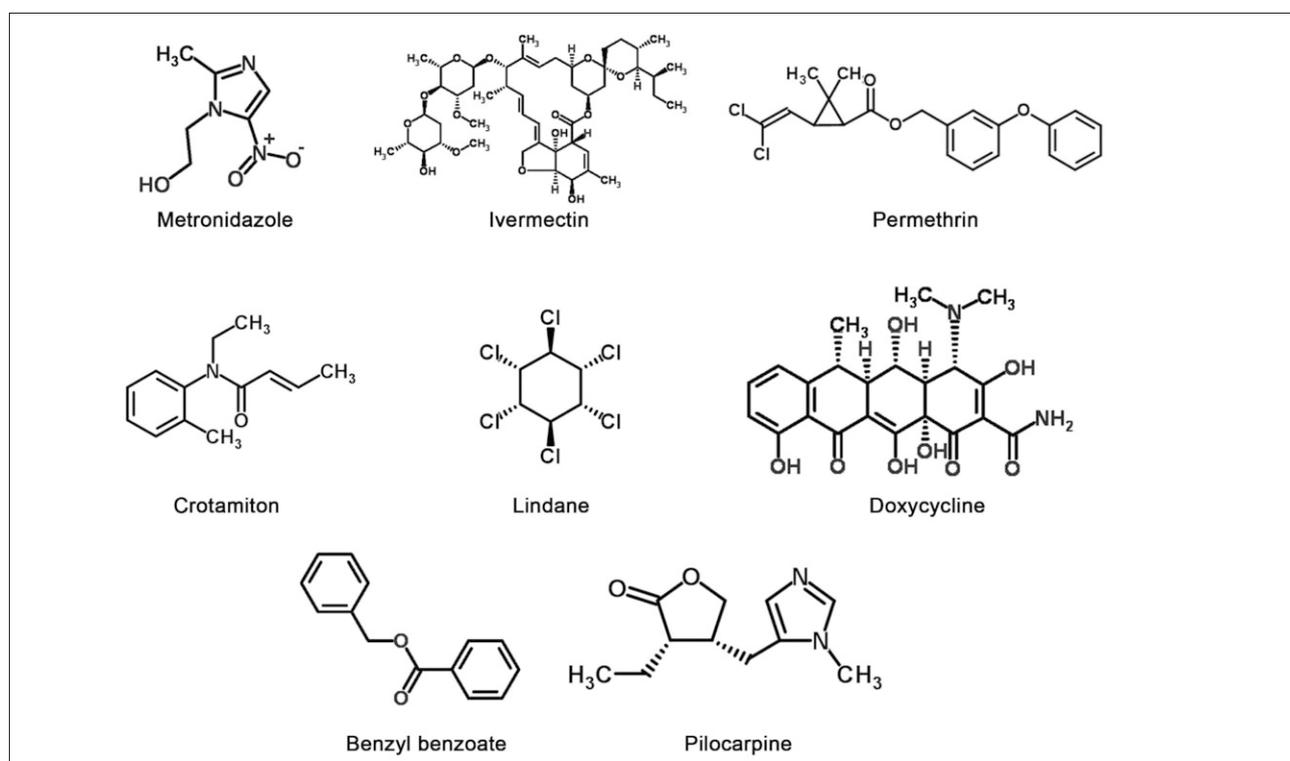


Figure 1. The chemical structures of metronidazole, ivermectin, permethrin, crotamiton, lindane, doxycycline, benzyl benzoate, and pilocarpine.

hypersensitivity.⁹ Systemic ivermectin treatment may result in transient and mild adverse reactions including anorexia, asthenia, headache, arthralgia, myalgia, fever, eosinophilia, and maculopapular rashes. Ivermectin should be avoided in pregnancy, breastfeeding, and infants weighing less than 15 kg. There has been one human ivermectin-resistant *Demodex* case reported.¹⁰

Permethrin

Permethrin is a type 1 topical synthetic pyrethroid agent, which is insecticidal and scabidical with low mammalian toxicity. Its anti-demodicidosis mechanism is unknown, but it can decrease *Demodex* mite count,¹¹ and improve dermatological signs and symptoms including erythema score.¹² Permethrin may slow the rate of closure of voltage-gated sodium channels of arthropods, leading to prolonged depolarisation of nerve cell membranes and disrupted neurotransmission, nerve depolarisation and hyper-excitation, and eventually to muscle paralysis and death. The neurotoxic effects of permethrin on vertebrates is relatively mild compared to invertebrates, due to the structural differences in voltage-gated sodium channels between vertebrates and invertebrates. Moreover, it may interfere with GABA receptor chloride ionophore complexes and neurotransmitters.¹³ Permethrin is poorly absorbed through the skin and the small percentage absorbed is then metabolised rapidly and excreted in the urine in the form of inactive metabolites. Adverse effects including pruritus, erythema, paraesthesia, headache, dizziness, muscle spasms, convulsions, and dystonic action of the neck have been reported. Topical use of permethrin is safe for pregnancy, breastfeeding, and infants over two months old.

Crotamiton

Crotamiton is a pale yellow oil with a fish-like odour used as an anti-scabies, anti-bacterial, and anti-pruritic agent for many dermatological

conditions. Crotamiton can reduce *Demodex* mite count¹⁴ and improve *Demodex*-related dermatological signs and symptoms. It is a common scabies treatment recommended for newborn babies and infants.¹⁵ The anti-pruritic effect is believed due to moderate TRPV-1 independent inhibition of histamine, serotonin, and PAR-2 agonist by crotamiton.¹⁶ Adverse effects include flushing, irritation, conjunctivitis, and contact dermatitis.¹⁵ It is safe in pregnancy, breastfeeding, and young infants.

Lindane

Lindane is an organochloride of the cyclohexane family, which acts on the GABA-gated chloride channels in arthropods, leading to paralysis and death of ectoparasites.¹⁷ Topical lindane treatment can reduce *Demodex* mite counts,¹⁸ and improve dermatological signs and symptoms.¹⁹ The adverse effects include dermatological symptoms such as irritation and allergic contact dermatitis, and neurological symptoms such as insomnia, irritability, vertigo, convulsions, restlessness, and collapse.¹⁵ Lindane should be avoided in pregnancy, breastfeeding, and infants.

Doxycycline, benzyl benzoate, and pilocarpine

Oral doxycycline is a broad spectrum bacteriostatic semi-synthetic antibiotic composed of a tetracycline nucleus with modified functional groups. Doxycycline inhibits the production and activity of matrix metalloproteinases (MMPs), especially MMP-9 directly and kallikrein (KLK) indirectly. Increased MMP-9 levels have been observed in patients with ocular rosacea, and doxycycline may be used to treat cases with recurrent corneal erosion. An *in vitro* study showed that human telomerase immortalized corneal epithelial cell line, exposed to *Demodex*-associated *Bacillus oleronius* proteins, can upregulate the expressions of pro-inflammatory mediators including IL-1 β , IL-6, IL-8, TNF- α , cathelicidin, MMP-3, and MMP-9.²¹ The chitin from exoskeleton of *Demodex* may activate TLR2 receptor in

keratinocyte, resulting in increased IL-8, TNF- α , cyclooxygenase-2, and inflammasome, which subsequently increase KLK-5, LL-37, cathelicidin, and MMP-9.²² Doxycycline can inhibit neutrophil activity and several pro-inflammatory mediators including phospholipase A2, endogenous nitric oxide (NO), TNF- α , IL-6, IL-8, and IL-10. In addition, the inhibition of NO synthase activity by doxycycline may explain the anti-inflammatory action in rosacea-associated vasodilation.^{22,23} Sub-antimicrobial dosing of doxycycline of under 50 mg/day (e.g. 20 mg b.i.d or 40 mg q.d.) was as effective or more effective than antimicrobial dosing (≥ 50 mg) in decreasing the release of pro-inflammatory cytokines and downregulation of ROS production, and was associated with much fewer adverse effects such as nausea, diarrhoea, and a lower risk of bacteria resistance.²⁴ The adverse effects of doxycycline include oesophageal erosion, gastrointestinal discomfort, and photosensitivity. Doxycycline is not recommended in pregnancy, breastfeeding, and infant.

Benzyl benzoate

Benzyl benzoate is an organic ester that is neurotoxic to the mites and is active against their ova.²⁵ Topical use can reduce *Demodex* mite counts and improve dermatological signs and symptoms. Adverse effects in high strength (greater than 25%) include transient skin irritation, burning sensation, and post-treatment eczematous reaction.²⁶ Topical use of benzyl benzoate is safe during the second or third trimester of pregnancy, breastfeeding, and in children older than one year of age.²⁷

Pilocarpine

Pilocarpine is a cholinergic parasympathomimetic agent acting as a non-selective muscarinic agonist. Pilocarpine can reduce the number of mites and alleviate the related symptoms.²⁸ No side-effects were observed after administration of pilocarpine to the lid margins only. Pilocarpine is not recommended during pregnancy, and the use of pilocarpine in breastfeeding and young children should be with caution.²⁹

Other topical treatments

Many topical treatments have been found to be useful for relieving or controlling human *Demodex* conditions. These include 0.01-0.02% hypochlorous acid, 99.9% ethyl-ether solution, 2% mercury oxide ointment, 100% alcohol, 6% sulphur lotion, camphorated oil, salicylic acid cream, azithromycin,³⁰ erythromycin, sodium sulphacetamide, and tretinoin. Many of these treatments when used alone are often not sufficiently effective in managing the condition.

Combination therapy

There are several trials of combination regimens for human demodicidosis. The oral metronidazole and ivermectin combined therapy showed significant reduction in mite count in acne, perioral dermatitis, anterior blepharitis, and rosacea groups compared to oral ivermectin alone. Moreover, this regimen was significantly better at reducing the mite count to the normal level in the rosacea and anterior blepharitis groups.³¹ Oral metronidazole and ivermectin combination therapy also showed subjective and objective improvement in blepharitis.³² The oral and topical metronidazole combination treatment showed excellent response to the fulminant rosacea-like eruption with multiple *D. folliculorum* mites. Dermatitis gradually cleared within one month, and the residual erythema on the patient's cheek resolved nine months later. In addition, a trial of combined oral metronidazole and prednisolone for three weeks in conjunction with topical metronidazole and lindane emulsion showed gradual reduction in pustules in tubercous pustular demodicidosis.³³ By using topical and oral metronidazole treatments for two months and yellow mercury ointment for 15 days, facial mites disappeared with complete remission without recurrence of rosacea-like demodicidosis.³⁴ Satisfactory results were achieved with no observable side-effects by topical camphor oil and oral metronidazole tablet given for 15 days. When oral ivermectin and topical permethrin treatments were used to acute lymphoblastic leukaemia-associated demodicidosis, no adverse effects were

experienced and the eruption resolved five weeks later. An oral ivermectin and topical permethrin combination regimen was also effective for rosacea-like folliculitis.³⁵

Conclusion

To control symptoms and achieve remission in demodicidosis, treatments should focus on reducing the mite count below a symptomatic threshold and restore the dermatological and ocular ecology to a balanced state, rather than complete mite eradication. Metronidazole, ivermectin, and permethrin have shown promising results in reducing the mite counts and relieving dermatological symptoms in *Demodex* infections. However, the repeated use of these drugs may result in the development of resistance. In refractory cases such as immunocompromised or systemic disease patients, combination therapies may be needed to relieve the symptoms and prevent recurrence. Therefore, further studies are needed to understand their mechanisms of action and toxicities, determine optimum dosage and length of treatment, and ultimately develop safe and effective therapies for human demodicidosis.

Conflicts of interest statement

The authors have no conflicts of interest to declare.

Financial support

Research reported in this publication was supported in part by the Natural Science Foundation of China (no. 81471973), the 2016 Medical Education Research Project of Chinese Medical Association Medical Education Branch and China Higher Education Society of Medical Education Professional Committee (2016B-KY013), and the Education and Teaching Reform Project of Sun Yat-sen University, China (2016).

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