

Choosing Treatment for Dogs With Generalised Demodicosis – Isoxazolines or Imidacloprid and Moxidectin?

A Knowledge Summary by

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PICO question

In dogs with generalised demodicosis, are isoxazolines as effective as a combined formulation of imidacloprid and moxidectin at reducing mite count and the severity of associated clinical signs?

Clinical bottom line

Five single-blinded, randomised, positive control trials, most under laboratory conditions, directly compared the use of isoxazolines against moxidectin/imidacloprid to treat canine generalised demodicosis. All of them showed comparable efficacy of isoxazolines. Three different isoxazolines were studied with two routes of administration (oral and topical) and four different dosing frequencies of moxidectin/imidacloprid. This made the papers more challenging to compare however, the evidence provided is sufficient to support their use. All of these trials were sponsored by the manufacturers of their respective isoxazoline products which may bias the study design and reporting of results. It is worth noting that sarolaner (Simparica™, Zoetis UK) was licensed in the UK for the treatment of canine demodicosis in January 2018 and that in the UK the Cascade should be followed when prescribing treatments. The licensed use of isoxazolines in other countries is beyond the scope of this article and the reader is urged to check local regulatory body advice before prescribing the below medications.

Clinical scenario

A seven-year-old male, neutered, long-haired, cross breed dog presented with a one month history of erythema, patchy alopecia and follicular casts to the feet, hindlimbs and dorsum. He had not been regularly treated with ectoparasiticides and had no previous history of skin disease. Deep skin scrapings from the affected areas revealed two to eight live *Demodex canis* mites per slide. Cytology showed mild numbers of surface cocci only with no inflammatory cells. His clinical exam was otherwise unremarkable and full blood count, biochemistry and urinalysis were within reference intervals.

The evidence

A recent systematic review by Perego et al. (2019) found good evidence for the use fluralaner and sarolaner with a good level of efficacy and safety, although long term follow up was lacking. They also found good evidence for the use of moxidectin/imidacloprid and noted improved efficacy with increased frequency of application (Perego et al., 2019). Moxidectin with imidacloprid is a good choice of positive control as it is a commonly used, licensed product for the treatment of canine demodicosis in the UK. Amitraz (Aludex®, MSD Animal Health) is also licensed for this purpose in the UK but is less commonly used as it is more difficult to get hold of, is more labour intensive and Perego et al. (2019) found insufficient evidence for its use. There is good evidence for the use of other treatment options that are not licensed in the UK for demodicosis, but may be licensed in other countries, such as milbemycin oxime and doramectin (Perego et al., 2019). Ivermectin has been used with good efficacy however, adverse effects are common and can be severe (Perego et al., 2019). The five papers found were all single-blinded, randomised positive control trials with four performed under laboratory conditions. They all directly compared isoxazoline ectoparasiticides to moxidectin combined with imidacloprid. Whilst the studies were small and their power was not calculated, they provide good evidence for the comparable efficacy of isoxazolines as a treatment for canine generalised demodicosis (Perego et al., 2019). None of these studies calculated confidence intervals and this would have strengthened the evidence

they provide. Four of the five were also performed under laboratory conditions which may not represent conditions in the general population.

Summary of the evidence

Becskei, C., Cuppens, O. and Mahabir, S. P. (2018)	
Population:	<p>Client owned dogs with clinical signs of generalised demodicosis that showed:</p> <ul style="list-style-type: none"> - Skin lesions on at least five body regions, entire body or pododemodicosis - At least four live <i>Demodex canis</i> mites found on skin scrapings <p>Patients were excluded if they were pregnant, lactating, intended for breeding, receiving immunosuppressive therapy, receiving systemic or topical antimicrobials, had been treated with an ectoparasiticide with residual activity against <i>Demodex canis</i>, had <i>Sarcoptes scabiei</i> mites or were under 8 weeks of age. The study population was recruited from centres in France, Hungary, Portugal and Italy.</p>
Sample size:	81 dogs
Intervention details:	<ul style="list-style-type: none"> - Patients were split into two groups in a ratio of 2:1 - 53 dogs received sarolaner, 28 moxidectin/imidacloprid - A randomised (one-way) block design was replicated in multiple clinics - 53 dogs received sarolaner <i>per os</i> at 2–4 mg/kg on days 0, 30 and if necessary 60, 90, 120 and 150 - 28 dogs received a topical application of moxidectin combined with imidacloprid at a minimum dose of 10 mg/kg and 2.5 mg/kg respectively given monthly, or weekly in severe cases - The severity of demodicosis was evaluated at every monthly visit
Study design:	Single-blinded, randomised non-inferiority trial
Outcome studied:	<p>The non-inferiority of sarolaner compared to moxidectin/imidacloprid</p> <p>Objective – number of live <i>Demodex canis</i> mites found in five deep skin scrapes taken from the same sites</p> <ul style="list-style-type: none"> - The sites were selected based on clinical exam. Areas that had primary lesions and showed the most severe evidence of current mite infestation were chosen - Approximately 1 cm² of skin was sampled at each site - A one-sided 97.5% exact lower confidence limit for the difference between cure rates for each treatment group was used to assess non-inferiority of sarolaner at the 0.025 one-sided significance level at days 30 and 60

	<ul style="list-style-type: none"> - A non-inferiority margin of 15% was used <p>Subjective – the severity of clinical signs was graded</p> <ul style="list-style-type: none"> - Absent - Mild (small body area affected, low intensity) - Moderate (great intensity and density of lesions over a small area) - Severe (great intensity and density of lesions over a large area)
<p>Main findings: (relevant to PICO question):</p>	<ul style="list-style-type: none"> - The parasitological cure rate for sarolaner was non-inferior to moxidectin/imidacloprid on day 60 but not day 30 (based on a present non-inferiority margin of 15%) - There was no significant difference between cure rates for treatment groups on days 30 or 60 - 100% of dogs receiving sarolaner that completed the study (53/53) achieved parasitological cure - 88.9% of the moxidectin/imidacloprid dogs that completed the study (24/27) achieved parasitological cure, one dog was withdrawn due to lack of efficacy at day 146 - The percentage reduction in mean mite counts for sarolaner was non-inferior to moxidectin/imidacloprid at days 30 and 60 - At day 90 (when approximately 80% of each group was still analysed) the total body area affected was 5% in the sarolaner group and 10% in the moxidectin/imidacloprid group - No adverse events were associated with either treatment
<p>Limitations:</p>	<ul style="list-style-type: none"> - Two of the dogs in the sarolaner group received systemic antibiotics during the trial and this may have hastened the improvement in their skin lesions, the authors do acknowledge this - Moxidectin/imidacloprid is licensed to apply once monthly although the data sheet notes (Advocate™ Spot-on solution, Bayer PLC, as published in the National Office of Animal Health (NOAH) Compendium 2019) that, at the case vet's discretion, it can be applied weekly to treat demodicosis - Weekly treatments were administered at home by the owner, this may have led to variability in the dose received by the patient due to accuracy of application - Dogs in the moxidectin/imidacloprid group had different dosing intervals based on the severity of their condition, this may have added variance to the results - The authors state that sarolaner appears to be at least as good as or better than most other miticides however, their study only proves non-inferiority not that sarolaner is a superior treatment

	<ul style="list-style-type: none"> - Ideally investigations for underlying disease should have been performed prior to enrolment e.g. blood and urine tests - Information regarding the age, breed and other baseline characteristics for each animal was not provided other than that they were over 8 weeks - There is no calculation of the power of the study or explanation why a ratio of 2:1 was chosen - Confidence intervals are not calculated - No justification for using mean rather than median age - It is unclear if animals were assessed by one or multiple assessors - All the authors were employees of Zoetis UK who manufacture sarolaner (Simparica™)
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Six R. H. et al. (2016)	
Population:	<p>Dogs with naturally occurring <i>Demodex canis</i> infestations that showed clinical signs of generalised demodicosis (alopecia, erythema, comedones, papules and pustules, casts, scales or crusts that involved five or more body regions or pododemodicosis).</p> <ul style="list-style-type: none"> - At least four live <i>Demodex canis</i> mites seen on deep skin scrapings - Dogs were not treated with an ectoparasiticide for at least 90 days prior to the study - They had not received a short acting corticosteroid for 1 week prior or a long acting corticosteroid for 4 weeks prior - The dogs were recruited from South Africa, they were 'locally sourced' mongrels over 6 months of age
Sample size:	16 dogs
Intervention details:	<ul style="list-style-type: none"> - Dogs were housed individually - 8 dogs were allocated to each group - Dogs were fed a commercial dry food for the duration of the study and given water ad lib - Dogs were acclimatised to the study conditions for at least 14 days before the first treatment was administered - Dogs were randomly allocated by ranking of mite count - Sarolaner was given <i>per os</i> at a dose rate of 2 mg/kg (tablets were shaved/sanded to aid accurate dosing) on days 0, 30 and 60 - Moxidectin/imidacloprid was applied topically at a minimum of 10 mg/kg and 2.5 mg/kg respectively given once weekly from day 0–81 - Deep skin scrapings were taken from five sites showing the most severe clinical signs based on visual examination

	<ul style="list-style-type: none"> - The same sites were scraped each time - Clinical signs were assessed through surface area affected by: comedones/pustules/papules, casts/crusts/scales, alopecia and erythema - Examination and skin scraping was performed on days 14, 29, 44, 59, 74 and 91 - The assessors were blinded to treatment group
Study design:	Single-blinded, randomised positive control trial under laboratory conditions (it is not stated if this is a superiority or non-inferiority trial)
Outcome studied:	<p>Objective – live mite counts</p> <ul style="list-style-type: none"> - Mite counts were transformed by $\log_e(\text{count} + 1)$ prior to analysis to remove excessive variance - Differences were assessed at the two-sided significance level $\alpha = 0.05$ - Geometric means were calculated from the least square means and used to minimise extreme outliers - One dog was excluded from the moxidectin/imidacloprid group due to an accidental laceration requiring antibiotic treatment
Main findings: (relevant to PICO question):	<ul style="list-style-type: none"> - Both treatments reduced live mite counts post-treatment compared to pre-treatment counts ($P < 0.0001$) - This was more rapid for the sarolaner group with a significant difference at day 14 ($P = 0.0331$) and day 29 ($P = 0.0038$) compared to the moxidectin/imidacloprid group - Mean counts were not significantly different after this - At day 44 100% of sarolaner treated dogs had negative scrapes - At day 59 100% of moxidectin/imidacloprid treated dogs had negative scrapes - Comedones, papules and pustules had resolved by day 29 in both groups - Casts, crusts and scales had resolved in seven dogs in each group by study completion - One sarolaner and two moxidectin/imidacloprid treated dogs still showed erythema and alopecia at the end of the trial - Total area affected by lesions reduced from 65% pretreatment to 1–2% at study completion - No adverse events were associated with either treatment
Limitations:	<ul style="list-style-type: none"> - Information regarding the age, breed and other baseline characteristics for each animal was not provided - It was not explained how the surface area affected was calculated

	<ul style="list-style-type: none"> - Dogs were examined clinically and considered in good health but there is no information as to how this was established e.g. were blood or urine tests performed to rule out underlying disease - Dogs were kept under laboratory conditions which may not be representative of a clinical scenario - The sample size is small, there is no calculation of power or how the sample size was reached, this may have affected the outcome - Confidence intervals are not calculated - It is unclear where these dogs came from raising ethical concerns enrolling them in the study as there is no mention of owner consent, if there was any financial gain or if they are strays - It is not clear how dogs were randomly allocated to the two treatment groups or if they were evenly distributed based on mite count - All of the authors were employees, directly or indirectly of Zoetis UK who manufacture sarolaner (Simparica™) - Another arm of this study involved infecting purpose bred laboratory Beagles with <i>Otodectes cynotis</i> and the control group were given a placebo treatment which represents a potential welfare issue for these dogs
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Fourie J. J. et al. (2015)	
Population:	Client owned dogs with naturally occurring generalised demodicosis that showed clinical signs (erythema, alopecia, comedones, follicular casts and crusts) and <i>Demodex canis</i> mites found on deep skin scrapings. Patients were otherwise healthy and had not been treated with a glucocorticoid or miticide for at least 12 weeks prior to the study. The study was conducted in South Africa.
Sample size:	16 dogs
Intervention details:	<ul style="list-style-type: none"> - Dogs were housed separately during the study period and were fed once daily and given water ad lib - 8 dogs were allocated to each treatment group - Dogs were acclimatised to their new housing for at least 14 days before the study commenced - All dogs were treated with a subcutaneous injection of cefovecin on days -14, -1, 13 and 27 for the treatment of pyoderma - Deep skin biopsies were taken from all dogs on days -14 and 27 - Group 1 were treated with fluralaner at a minimum dose of 24 mg/kg on day 0

	<ul style="list-style-type: none"> - Group 2 were treated with 2.5 mg/kg moxidectin/10 mg/kg imidacloprid topically according to the manufacturer's guidelines on days 0, 28 and 56 - Deep skin scrapings were taken from an area approximately 4 cm² from five sites on days -4, 28, 56 and 84 and the same sites were sampled each time - Clinical signs were assessed on days -4, 28, 56 and 84, the body areas affected were sketched on a silhouette - Lesions recorded: erythema, casts, scales, crusts, alopecia - Percentage of hair regrowth was estimated - Colour photographs were taken to help compare lesions at each assessment
Study design:	Single-blinded randomised positive control trial under laboratory conditions (it is not stated if this is a superiority or non-inferiority trial)
Outcome studied:	<p>Objective – mean mite number on skin scrapings</p> <ul style="list-style-type: none"> - Efficacy was calculated using geometric means and Abbot's formula - The groups were compared using an analysis of variance test (ANOVA) with a treatment effect after a logarithmic transformation of the mite (count + 1) data for each study day <p>Subjective – improvement in clinical signs</p>
Main findings: (relevant to PICO question):	<ul style="list-style-type: none"> - Fluralaner reduced the mean mite number by 99.8% on day 28 and 100% on days 56 and 84 - Moxidectin/imidacloprid reduced the mean mite number by 98% on day 28, 96.4% on day 56 and 94.7% on day 84 - P values were: day 28 = 0.0917, day 56 = <0.0001, day 56 = 0.0020 - There was a significant difference between fluralaner and moxidectin/imidacloprid on days 56 and 84 - Both groups showed improvements in clinical signs - No adverse events were associated with either treatment
Limitations:	<ul style="list-style-type: none"> - Moxidectin/imidacloprid was used at the licensed dosing interval however, the data sheet (Advocate™ Spot-on solution, Bayer PLC, as published in NOAH Compendium 2019) states that for the treatment of demodicosis it can be used weekly at the case vet's discretion. This may have affected the treatment response in this study - There is limited information regarding the statistical analysis of the data (e.g. statistical package used, ANOVA assumptions) and only geometric mean mite counts were provided - Information regarding the age, breed and other baseline characteristics for each animal were not provided

	<ul style="list-style-type: none"> - Dogs were kept under laboratory conditions which may not be representative of a clinical scenario - The authors state the dogs were 'healthy as far as could be determined' but do not clarify what tests were performed - One of the dogs was withdrawn from the moxidectin/imidacloprid group on day 59 due to the development of malignant lymphoma but the data before this date was included in the trial. This may have affected the treatment response for this group - Ideally antibiotics should have been used based on skin cytology and presence of pyoderma, presumably blanket treatment was chosen to avoid variance - A sample size of 16 dogs is small and there is no justification of this or calculation of the power of the study. This may have affected the results - Confidence intervals were not calculated - There was no information on recruitment measures (e.g. financial incentives) or source of cases - Five of the six authors were employees, directly or indirectly of MSD Animal Health the manufacturers of fluralaner (Bravecto®)
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Beugnet, F. et al. (2016)	
Population:	Client owned dogs over 6 months of age that showed signs of generalised demodicosis on days -14, -7, and -2 or -1. All dogs showed lesions (erythema, crusts, scales, alopecia, comedones or follicular casts) on either at least five body regions, an entire body region or two or more feet. All dogs had <i>Demodex canis</i> mites confirmed on deep skin scrapings on day -1. None of the dogs were pregnant or had been treated with a glucocorticoid or ectoparasiticide for 12 weeks prior to the study. Antibiotics and vitamin/mineral supplements were allowed during the trial. Dogs were leased from their owners and recruited from South Africa.
Sample size:	16 dogs split
Intervention details:	<ul style="list-style-type: none"> - Dogs were randomised into treatment groups by ranking of pre-treatment mite counts and sex and 8 dogs allocated to each group - Dogs were housed in separate pens, fed once daily and water was given ad lib. They were moved to this housing for at least 14 days prior to the start of the study - Group 1 received afoxolaner and group 2 moxidectin/imidacloprid both dosed according to the manufacturer's guidelines. No further information on dosing was provided

	<ul style="list-style-type: none"> - Doses were given on days 0, 14, 28 and 56 - Mite counts and clinical exams were performed on days 2, 28, 56 and 84 - Skin scrapings were taken from the same five sites at each exam - A sketch was made of the body areas affected by: erythema, casts/scales/crusts, and alopecia. Colour photographs were taken on days -2, 28, 56 and 84
Study design:	Single-blinded, randomised positive control trial under laboratory conditions (it is not stated if this is a superiority or non-inferiority trial)
Outcome studied:	<p>Objective – mean mite counts</p> <ul style="list-style-type: none"> - The group mean, median, standard deviation, geometric mean, minimum and maximum counts were calculated - Pre and post-treatment administration mite counts were compared using ANOVA and a significance level of 5% was set <p>Subjective – clinical lesions and hair regrowth</p>
Main findings: (relevant to PICO question):	<ul style="list-style-type: none"> - There was a significant ($P < 0.05$) reduction in mite count for both groups on all post-treatment assessments - Group 1 (moxidectin/imidacloprid) mite count reduced from a geometric mean of 808.1 before treatment to 82.4-119.9 after one month - Group 2 (afoxolaner) mite count reduced from a geometric mean of 650.8 before treatment to 0.0-5.3 after one month - There was no significant difference in mean mite count ($P = 0.8103$) between the groups at the start of the trial - Significantly fewer mites were found on all post-treatment assessments for the afoxolaner group compared to the moxidectin/imidacloprid group ($P < 0.05$) - Both groups showed improvements in clinical signs but no resolution of them - No adverse events were associated with either treatment
Limitations:	<ul style="list-style-type: none"> - The dosing interval of moxidectin/imidacloprid was every 2 weeks for three doses then every 4 weeks. The authors acknowledge that weekly treatment, as suggested in the manufacturer's guidelines, may have improved treatment outcome but do not state why they chose not to treat at this interval - The authors chose eight dogs per group as it was higher than the six recommended by the Committee for Medical Products for Veterinary Use guideline but do not calculate the power of the study - Confidence intervals were not calculated

	<ul style="list-style-type: none"> - Limited information is provided on statistical analysis e.g. ANOVA assumptions - Dogs were leased from their owners indicating a financial gain and potential ethical implications - Afoxolaner was used off license at 2 weekly intervals, they acknowledge that further study of monthly administration is warranted - The dogs were split into blocks of two based on sex and mean mite count, it is not clear if they were then randomly allocated to the two treatment groups or evenly distributed based on mite count - Dogs were kept under laboratory conditions which may not be representative of a clinical scenario - Information regarding the age, breed and other baseline characteristics for each animal is not provided - All of the authors were employees, directly or indirectly of Merial the manufacturer of Afoxolaner (NexGard®)
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Fourie, J. J., Meyer, L. and Thomas, E. (2019)	
Population:	Client owned dogs, between 6 and 12 months of age, with naturally acquired generalised demodicosis defined as: <ul style="list-style-type: none"> - More than five body areas affected, pododemodicosis involving two or more feet or an entire body region - Dogs must be older than 8 weeks - Acclimatised to the study site for at least 7 days - Presence of <i>Demodex canis</i> mites on skin scrapings on day 2 - Otherwise clinically healthy on days -7 and -2 - Not pregnant - Not treated with glucocorticoids, ectoparasiticide or macrocyclic lactone for at least 12 weeks - Not excessively fractious (safe for personnel)
Sample size:	16 dogs
Intervention details:	<ul style="list-style-type: none"> - Dogs were ranked by mite count then randomly allocated to 1 of 2 groups using MS Excel software, 8 dogs were allocated to each group - Age was assessed based on presence of permanent dentition - Dogs were transferred to the study site and housed individually indoors - Dogs were fed a commercially available dry dog food once daily with water ad lib - Group 1: 25 mg/kg fluralaner applied topically on day 0 - Group 2: At least 10 mg/kg imidacloprid and 2.5 mg/kg moxidectin applied topically on days 0, 28 and 56 - Four dogs in Group 2 were treated weekly rather than every

	<p>4 weeks (based on manufacturer's guidelines)</p> <ul style="list-style-type: none"> - Cases classified as mild, moderate or severe based on clinical condition (crusts, casts, scales, hair loss and erythematous papules) by blinded veterinarian and examinations performed every 2 weeks - All dogs were treated with cefovecin (Convenia®) for potential pyoderma on days -7, 7, 21, 35 and 49 and a probiotic (Protexin®) at least twice weekly - Skin biopsies were performed on days -7 and 27 to assess for <i>Demodex canis</i> mites, acanthosis, hyperkeratosis, surface crusting, pigmentary incontinence, follicular keratosis, mural folliculitis, perifolliculitis, dermatitis, bacteria, granulomas and dermal stromal reaction - Skin scrapings and mite counts were performed on days -2, 28, 56 and 84 and were blinded - Deep skin scrapings were taken from an area approximately 4 cm² at the same five sites for each dog on every occasion - Only live mites were recorded
Study design:	Single-blinded, randomised, non-inferiority trial under laboratory conditions
Outcome studied:	<p>Objective – percentage live mite reduction</p> <ul style="list-style-type: none"> - Arithmetic means for each group pre- and post-treatment - Repeated measures analysis of covariance (RMAN-COVA) was used to compare mite counts using SAS Institute analytical software version 9.3 - Significance level was set at 5% <p>Subjective – clinical signs</p> <ul style="list-style-type: none"> - Mild, moderate or severe - Based on crusts, casts, scales and erythematous papules as percentage of group affected - Areas of hair loss scored 1 (0-50%), 2 (>50-90%) and 3 (>90%)
Main findings: (relevant to PICO question):	<ul style="list-style-type: none"> - No treatment related adverse events were noted - Fluralaner was significantly more effective than moxidectin/imidacloprid at eliminating live mites from dogs with generalised demodicosis (P<0.01) - 0/8 dogs in group 1 had any live mites at day 84 - 1/8 dogs in group 2 was mite free at day 56 and 2/8 at day 84 - 2/8 dogs in group 2 showed an increase in live mite counts after treatment and this impacted significantly on efficacy calculations (based on mean mite counts for the group)
Limitations:	<ul style="list-style-type: none"> - Group 2 dogs received two different treatment regimes (weekly and four weekly application) but results were not

	<p>analysed separately</p> <ul style="list-style-type: none"> - All dogs were given 10 weeks of cefovecin regardless of the presence or absence of pyoderma, the authors note that diagnosis and treatment of pyoderma was not part of the treatment evaluation - Dogs were between 6 and 12 months of age indicating juvenile generalised demodicosis rather than adult onset which has the potential for self-resolution of signs, this may have affected results - The age, sex and breed of dogs in each group is not recorded - Dogs were ranked by mite count before being randomly allocated to treatment groups but the reason for ranking before randomisation is not clear - Dogs were kept under laboratory conditions which may not be representative of a clinical scenario - Ideally antibiotics should have been used based on skin cytology and presence of pyoderma, presumably blanket treatment was chosen to avoid variance - A sample size of 16 is small and there is no justification for this or calculation of the power of the study. This may have affected the results - Confidence intervals were not calculated - No criteria for treatment success were outlined and results were only provided for live mite counts (not clinical signs or histopathology) - No information on recruitment measures (e.g. financial incentives) or source of cases - It is unclear what the aim of the study was, the authors state 'to evaluate the efficacy... compared to moxidectin/imidacloprid' but not if this is an inferiority or superiority study however, the authors then state superiority in the results and discussion - All authors were employed (directly or indirectly) by MSD Animal Health, the manufacturer of fluralaner (Bravecto®) - Summaries of product characteristics for moxidectin/imidacloprid (Advocate® Spot-on solution, Bayer PLC) referenced are for cats and ferrets, not dogs
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Appraisal, application and reflection

Three different, widely available, isoxazolines were studied in these five papers, two focused on sarolaner, two on fluralaner and one on afoxolaner. All five studies were sponsored by the pharmaceutical companies that make the isoxazoline preparations and nearly all authors were employees of these companies. This may bias study design and reporting of results as demonstrated in the study by Becskei et al. (2018) where sarolaner is claimed to be as good as, if not better than moxidectin/imidacloprid, but the study was only

designed to prove non-inferiority. In each paper the dosing frequency of moxidectin/imidacloprid varied making them harder to compare. The license for this product is for monthly application, however, the data sheet (Advocate™ Spot-on solution, Bayer PLC, as published in NOAH Compendium 2019) states that it can be used weekly to treat canine demodicosis in more severe cases at the case veterinarian's discretion. Ideally all papers would have used weekly dosing intervals as this is more effective (Mueller et al., 2012, Perego et al., 2019). Monthly treatments may have only been successful in mild cases and this may be why Fourie et al. (2015) found such a significant difference between the two treatment groups.

Generalised adult onset demodicosis can be associated with immunosuppression. The cause of this may be difficult to identify but ideally a full blood count, biochemistry, urinalysis, lymph node aspirates, thoracic radiographs and abdominal ultrasound should be performed to rule out underlying conditions (Mueller et al., 2012). Hyperadrenocorticism and hypothyroidism are important disorders to investigate as part of this process (Mueller et al., 2012). The presence of an underlying condition could alter the treatment response and investigations should have been fully detailed or performed more thoroughly in these papers.

All of the papers show that isoxazolines are at least as effective as moxidectin/imidacloprid at reducing the mean mite count from deep skin scrapings. Deep skin scrapings are the gold standard diagnostic method to identify demodicosis and the area covered should be approximately 1 cm² and focused on primary lesions (Mueller et al., 2012). At least three to five areas should be sampled and this should be repeated until there are two consecutive negative scrapes one month apart (Mueller et al., 2012). Cytology should also be performed to identify the presence of pyoderma, a common complication of demodicosis (Mueller et al., 2012). Fourie et al. (2015) and Fourie, Meyer and Thomas (2019) treated all dogs with 8 weeks and 10 weeks respectively of a third-generation cephalosporin during the trial. This standardised treatment, but blanket antibiotic usage in these cases, would not be an advisable approach in practice. Identification of pyoderma on cytology and ideally of the bacteria involved through culture and sensitivity is recommended. Fourie, Meyer and Thomas (2019) took skin biopsies to assess for pyoderma however, they do not comment on the findings and note that it took 22 days for biopsy results to be available. As mentioned above, cytological evaluation and culture and sensitivity would have been a preferable method to assess for the presence of pyoderma.

All of these studies use relatively small numbers of patients and four of the five kept animals under laboratory conditions that are unlikely to replicate those of our patients. Confidence intervals are not calculated and some papers lack full detail regarding statistical analysis. Addressing all of these points may increase the strength of evidence provided. Another concern is the use of stray dogs and financial incentives to owners to enroll pets onto the treatment trials. This may compromise animal welfare through separation from owners, normal environments and routines. The Six et al. (2016) study also looked at the efficacy of sarolaner to treat artificial *Otodectes cynotis* infestations in laboratory Beagles. The control group in this arm of the trial was given a placebo treatment which again may compromise welfare.

A recent systematic review by Perego et al. (2019) found good evidence for the use of fluralaner and sarolaner in the treatment of generalised demodicosis. Afoxolaner showed good efficacy but only one study was found providing limited evidence for their use. Isoxazolines appear safe as well as efficacious, no adverse effects were noted in any of the studies reviewed here, but further long term follow up is required to confirm this.

Methodology Section

Search Strategy	
Databases searched and dates covered:	CAB Abstracts through CAB direct platform 1973 – week 9 2019 PubMed through NCBI 1900 – week 9 2019 Web of Science 1900 – week 9 2019 Scopus 1970 – week 9 2019
Search terms:	Dog or dogs or canine* or bitch* or bitches or canis AND Demodicosis or demodex or demodectic

	AND Isoxazoline or isoxazolines or fluralaner or sarolaner or afoxolaner or lotilaner AND Imidacloprid or moxidectin or advocate or advantage multi
Dates searches performed:	March 1 st 2019

Exclusion / Inclusion Criteria	
Exclusion:	Articles not available in English, narrative reviews, non-peer reviewed journals, book chapters, conference proceedings and articles that did not answer the PICO question
Inclusion:	Original, peer reviewed articles that compared isoxazolines with moxidectin/imidacloprid

Search Outcome					
Database	Number of results	Excluded - Review Articles	Excluded - Did not answer the PICO question	Excluded - Not available in English	Total relevant papers
CAB Abstracts	3	2	0	0	1
PubMed	8	1	2	0	5
Web of Science	11	1	5	0	5
Scopus	1	0	0	0	1
Total relevant papers when duplicates removed					5

CONFLICT OF INTEREST

The author declares no conflicts of interest.

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