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Morgellons disease etiology and therapeutic approach: a systematic review

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Abstract

Morgellons disease is characterized by patient reports of fibers embedded in and protruding from the skin. Etiologies from infection to delusion have been endorsed, and treatment guidelines are not well-defined. The objective of this manuscript is to evaluate the existing evidence regarding the etiology and treatment of Morgellons disease in an effort to better inform clinical management. A PubMed search including key words "Morgellons," "delusional parasitosis and fibers," "delusions of parasitosis and fibers," or "delusional infestation and fibers" was completed. Original publications directly assessing etiology or treatment methods of Morgellons disease published between January, 2010 and the time of manuscript preparation were reviewed and evaluated. Sixteen articles regarding etiology were reviewed. All studies were correlative in nature with various limitations. Support for a psychiatric etiology was more widespread than support for an infectious etiology. Eleven articles regarding treatment efficacy were reviewed. Antipsychotic regimens have the most evidence of efficacy. Existing data regarding Morgellons disease suggests a psychiatric etiology and supports treatment with a low-dose antipsychotic agent once non-psychiatric causes have been excluded.

Keywords: antipsychotics, Borrelia burgdorferi, delusional infestation, delusions of parasitosis, etiology, fibers, filaments, Morgellons, tick-borne

Introduction

Morgellons disease (MD) is a condition that has garnered significant media attention in recent years [1]. However, MD is not currently recognized by the medical community as a distinct clinical disorder with established diagnostic criteria. Although many cases of MD have been described, there is little consensus among patients, healthcare providers, and other researchers about several key features of the condition. Many clinicians treating these patients identify the disease as a subtype of delusional infestation because of an inability to identify an alternative cause, thereby classifying MD as a psychosomatic disorder [2]. As with other conditions with psychiatric contributions, it is often difficult for patients to reconcile their subjective experience with their providers' explanation. In addition to this conflict between patients and clinicians, there is dissent among the medical community. One research group has published several studies to support the theory that MD is infectious in nature rather than psychiatric [3]. Treatment is also contested, as there are currently no official treatment recommendations for MD given insufficient grounds to classify it as a distinct diagnosis. Many therapeutic strategies have been attempted [4-11]. Owing to various perspectives on this condition and its management, the purpose of this manuscript is to evaluate the existing evidence regarding both the etiology and treatment of MD in an effort to better inform clinical care.

Methods

PubMed searches including key words “Morgellons,” “delusional parasitosis and fibers,” “delusions of parasitosis and fibers,” or “delusional infestation and fibers,” with publication dates from January, 2010 to April, 2021 were considered for brevity (**Figure 1**), [12]. Additional records were identified by searching PubMed for specific articles referenced in these previously identified works. Articles not written in English were excluded owing to author limitations. Articles were screened for fully-accessible text. Full review of each publication was conducted by two reviewers. Articles were excluded if their reported cases did not specify infestation with an inanimate material such as fibers, fuzz, specks, threads, colored substance, or splinters or if they were not original investigations or observations directly addressing the pathophysiology of MD or the efficacy of MD treatment strategies. Data regarding pathophysiology including demographics, disease characteristics, psychiatric comorbidity, molecular test results, and histologic findings and treatment including attempted therapies, efficacy, dosing regimens, frequency, and adverse events were recorded. Twenty-five articles were selected and evaluated. The studies were graded according to the

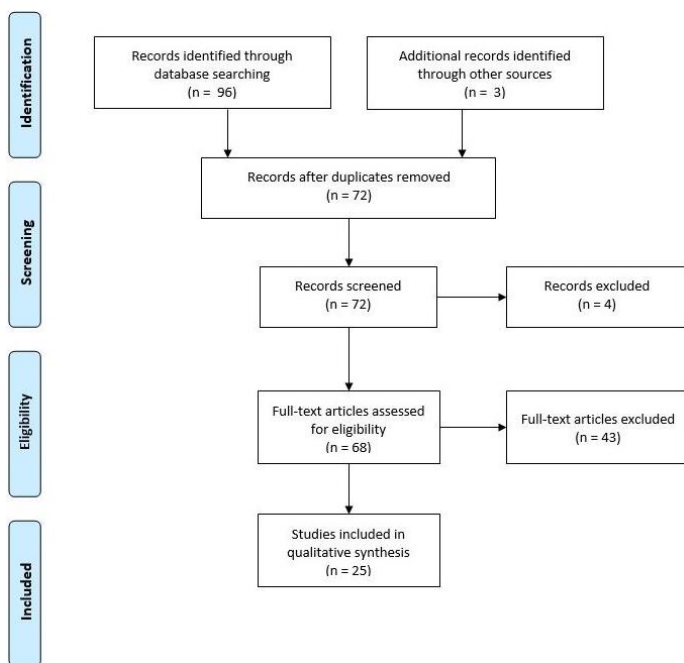


Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses diagram illustrating the article selection process [12].

Oxford Centre for Evidence-Based Medicine Levels of Evidence System [13]. Risk of bias in individual studies was assessed by examining the author associations and methodology. Selective reporting within studies and publication bias were considered to assess risk of bias across studies.

Results

Pathophysiology

In 2012, the Centers for Disease Control (CDC) performed the first population-based and most comprehensive study to date of patients exhibiting symptoms of Morgellons disease, such as patient-reported complaints of fibers along with abnormal skin sensation and/or lesions [14]. The study examined 115 case-patients in California with self-described MD. Several findings of this study support a psychiatric etiology of the condition with which these patients are afflicted (**Table 1**), [14]. The investigators did not find a pattern of clinical or epidemiological abnormality consistent with any specific infectious etiology. Lesions were sparse in areas not easily accessible by patients, histopathological features were consistent with chronic rubbing or excoriation without additional underlying etiology, and the most common sequence of symptom onset in this patient population was abnormal skin sensation prior to lesion and fiber appearance. These findings suggest that existing lesions in this study may be secondary to scratching with secondary contamination by fibers rather than spontaneous appearance. Compositional analysis of sampled material indicated that protein and cellulose were common components, consistent with skin fragments and textile fibers, respectively. This study also identified a correlation with neuropsychiatric comorbidity within the studied population [14]. There was evidence of psychoactive drug use in 50% of the participants, although it is unclear whether this behavior preceded MD onset or if it was a reaction to symptoms. A similar pattern of drug use was found in a retrospective chart review of 79 patients with delusional infestation treated at a tertiary care medical center in which 57% of patients under the age of 60 reported stimulant use [15].

There are several shortcomings of the CDC's study, but numerous smaller-scale studies have mirrored these findings and likewise favor MD to be a subtype of delusional infestation ([Table 2](#)), [10,11,16-19]. Although none of these studies were methodologically flawless, this collection of widespread findings supports that psychiatric disturbance plays a key role in the development of MD.

Others believe that MD is a cutaneous consequence of tick-borne spirochetal infection with a borrelial species such as *B. burgdorferi*. Sources endorsing this theory cite culture findings, histopathological evidence, and molecular evidence of infection with *B. burgdorferi* in specimens of MD patients ([Table 3](#)), [20-28]. With the exception of a single study authored by a frequent coauthor, studies in support of this theory to date have all been authored by Dr. Raphael Stricker—a past president of the International Lyme and Associated Disease Society [20-29]. Many of these investigations study MD patients with known borrelial disease and often reuse the same subjects across multiple publications [21-26].

The integrity of the CDC's findings suggesting the absence of infectious etiology in MD patients has been contested by those claiming a borrelial etiology. They criticized the fact that the CDC took cultures from only 28 of 467 originally identified patients and collected fibers from only 12 [3]. They do not consider the patients in the CDC study to be true MD patients, as fibers were not as embedded as necessary to meet their definition of a case [3]. Furthermore, they argue that the CDC's two-tiered serological testing was too insensitive to prove absence of *B. burgdorferi* in those with MD [3].

In respect to these criticisms, if none of the CDC's 115 case-patients with the prerequisite of belief of inanimate material infestation with lesions and/or disturbing skin sensation met the borrelial team's standards MD would be extremely rare [14]. Borrelial theorists earlier used a sample in which 58 of their 122 MD patients were from California and were predominantly middle-aged Caucasian females—the same geographic region from which the CDC study drew a similar demographic of patients [20].

They later reported that six percent of those with Lyme disease seropositivity in California—a condition with an estimated incidence in the US of greater than 300,000 a year—had MD [26, 30]. A failure of the CDC to include any true MD patients in light of these statistics is unlikely. The borrelial team's critique of serological testing implies that only their own detection methods are sensitive enough to detect *B. burgdorferi* as commercial serological tests used by the CDC have lower sensitivity ranging from 46% to 99% [31]. Even with this level of sensitivity, association between MD and *B. burgdorferi* as strong as claimed would likely result in more convincing evidence than a single borderline positive test. Furthermore, a positive molecular result for *B. burgdorferi* in the absence of seropositivity has great potential to represent a false positive and would be of little significance in the CDC's study [32]. This same risk is one possible explanation for some of Middelveen et al.'s positive test results.

Treatment

Treatment of MD can be challenging owing to the lack of standardized treatment guidelines stemming from unclear categorization of the disease [33]. Patients also may be resistant to treatment, as the prevailing belief that the condition is psychosomatic in nature leads to prescription of psychiatric medications. This is generally incompatible with the patient's subjective experience and conviction of skin disease. It is typical for these patients to bounce around among different physicians in search of a definitive treatment for their symptoms that is congruent with their expectations [34].

From case report data, low-dose antipsychotics along with adjunctive therapy of antibiotics, antihistamines, and anti-depressive agents as needed have the most evidence for effectively alleviating the symptoms of Morgellons ([Table 4](#)), [11, 35]. Although first-generation antipsychotics are associated with higher rates of ocular and extrapyramidal symptoms than second-generation antipsychotics, the low doses of first-generation antipsychotics used for symptomatic management of Morgellons have a relatively low reported incidence of adverse effects, with the most common complication being fatigue [5]. A growing body of

evidence supports the efficacy of low-dose second-generation antipsychotics in symptomatic relief of MD as well, making this a reasonable treatment option for those who are uncomfortable with the increased potential for adverse effects associated with first-generation antipsychotics [6-11]. Patients can be started on a low dose of the chosen antipsychotic agent at bedtime and be monitored for tolerance with gradual drug titration if symptomatic improvement is not achieved after two months and the patient remains free of adverse effects. Frequent follow-up is extremely important with MD patients: once-weekly phone calls, two-to-four-week follow-up office visits, and other checks of medication adherence can improve treatment success [35]. After stabilization, patients can be seen every three or four months. If the patient wishes to discontinue the medication, a taper can be attempted; if symptoms recur, the taper is discontinued and the patient is maintained on their minimum effective dose [33].

Although antipsychotic mediations have been effective in relieving symptoms of MD, patients are often hesitant to accept that there is any psychiatric component to their disease and are reluctant to initiate antipsychotic therapy. Comorbid depression, anxiety, and substance use disorders in MD patients often complicate treatment. A strong patient-physician relationship and a team-based approach can be beneficial in these situations [10]. By emphasizing the antipruritic and analgesic properties of some antipsychotics, acknowledging the frustration of the patient, and avoiding the characterization of the patient as delusional, the physician can decrease the patient's feelings of stigmatization and strengthen trust between patient and physician.

Discussion

Etiology and treatment of MD are highly contested. Although there is not yet evidence conclusively supporting a causative relationship between MD and psychiatric disease, more widespread correlative evidence supports the categorization of MD as a subtype of delusional infestation. High rates of psychiatric comorbidities in MD patients have been reported in several publications—consistent with

findings in general delusional infestation [11,14-17]. Several studies attempt to offer support for an infectious process, but the majority of these publications are authored by one team of researchers; a considerable quantity of reported data is drawn from a handful of repeatedly studied patients with known intersection of Morgellons disease and *Borrelia* exposure [21-26]. Improper research techniques and skewed correlations should be considered when interpreting the findings in support of a borrelial etiology. Selective suppression of contradictory data may also be a concern [36]. A research team entirely independent of the researchers discussed above has yet to find a relationship between *B. burgdorferi* and MD [10,11,14,16,18,19]. Many treatment plans for MD have been attempted with varying degrees of success in alleviating symptoms. However, administration of low-dose antipsychotics is the most widely supported strategy [4-11].

Limitations of these conclusions include the possibility that the label of Morgellons disease defined by skin disturbance and fiber growth is currently being applied to a heterogeneous group of patients. A blinded assessment of clinical and histological findings in Morgellons disease patients with and without evidence of *B. burgdorferi* exposure may be useful to determine whether two clinically distinct populations exist. In respect to etiologic investigations, cause and effect cannot be definitively demonstrated by the case studies and case series currently available. Evidence of a psychological etiology of MD is particularly difficult to demonstrate with this format given delusional infestation's status as a psychosomatic disorder and thus a diagnosis of exclusion. In respect to treatment, publication bias favoring treatment attempts resulting in resolution may have resulted in a skewed representation of therapy efficacy.

Conclusion

Despite numerous attempts to elucidate the pathophysiology of MD and the most successful treatment strategy for it, there remains a lack of certainty regarding either of these aspects owing to a paucity of well-designed investigations. Available

data favors a psychosomatic etiology and treatment with a low-dose antipsychotic regimen. Although it seems that MD patients may only perceive infestation with fibers, they undoubtedly suffer greatly with their condition. Combining a more widespread understanding of the disease and its treatment with an empathetic approach that acknowledges the patient's distress is essential in alleviating the physical and psychological burdens of this disease.

Potential conflicts of interest

Steven Feldman has received research, speaking and/or consulting support from a variety of

companies including Galderma, GSK/Stiefel, Almirall, Leo Pharma, Boehringer Ingelheim, Mylan, Celgene, Pfizer, Valeant, Abbvie, Samsung, Janssen, Lilly, Menlo, Merck, Novartis, Regeneron, Sanofi, Novan, Qurient, National Biological Corporation, Caremark, Advance Medical, Sun Pharma, Suncare Research, Informa, UpToDate and National Psoriasis Foundation. He is founder and majority owner of www.DrScore.com and founder and part owner of Causa Research, a company dedicated to enhancing patients' adherence to treatment. Katherine Beuerlein and Esther Balogh have no conflicts to disclose.

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Table 1. Summary of investigative measures and associated findings from the Centers for Disease Control and Prevention [14].

Measures	Findings
Cases per month within the Kaiser Permanente of Northern California system	3.65 per 100,000 enrollees with 115 case patients identified for further investigation
Epidemiology via electronic patient survey	Higher rates in females and 45-65 age group Most commonly reported fibers (70%) as the emerging material
Symptoms, habits, and exposures via electronic patient survey	Initial symptom most often disturbing skin sensations followed by lesions and/or solid material (56%) 86% of fibers detected by patients are on areas of abnormal skin sensation 73% of patients reported fibers or solid materials emerging from unbroken skin Fatigue and musculoskeletal complaints were the most commonly reported non-skin symptoms, affecting ~70% of patients each
Electronic Likert scale rating of skin symptom severity by patients	60% of patients ranked severity as a 5/10 or greater in severity, with 10 being most severe. 37% reported fiber/material currently emerging from the skin 61% reported fiber/material emergence within the 24 hours prior to assessment
Health-related Quality of Life via electronic patient survey	Patients reported higher rates of "fair" or "poor" health status (>50%) than California residents in general
Medical history and general physical exam	41 patients representative of the overall cohort underwent in-person clinical evaluation
Overall skin condition and distribution via standardized form administered by a dermatologist	Lesion presentation varied substantially—many lesions were crusted, and some were ulcerated or eroded A median of 17 lesions were documented per patient, with forearms, back, chest, face, and lower legs as common locations Back lesions tended to spare dumbbell-shaped area in the center of the back Lesions resembled those caused by chronic irritation and excoriation
Photographs of biopsy sites under dermatoscopy	Featured photos displayed visible fibers and were indicated to be representative of observed skin lesions
Neurocognitive and neuropsychiatric assessment with standardized battery of exams	Fully completed in 36 of the 41 patients undergoing clinical evaluation 59% had cognitive impairment in at least one area, most commonly in attention and memory Of 24 patients with somatic complaints, 50% had scores indicating severe impairment, 39% had co-existing depression, 37% had other neuropsychiatric conditions
Histopathologic examination of biopsies of abnormal-appearing or abnormal-feeling skin under light microscopy by two dermatopathologists blinded to diagnosis and under polarized light by a pathologist with special stains for inflammatory infiltrates and confirmatory immunohistochemical stains or polymerase chain reaction assays when indicated	31 of 41 case patients had biopsiable lesions or material present on skin 62 biopsies were taken: 37 from lesions, 22 from normal skin, and 3 from unknown locations Solar elastosis as most common finding in lesions at 51% Biopsied lesions showed evidence of excoriation or chronic irritation in 40% and evidence of arthropod bite or drug allergy in 16% Biopsies of non-lesioned skin were largely histologically normal with 23% of these biopsies having fibers composed of cellulose adjacent to or at the edge of the biopsy and one biopsy containing material consistent with a resorbable suture
Microbiologic analysis of open skin lesions	28 patients had purulent lesions which were swabbed Bacteria grew from lesions of 15 patients, all of which had histopathologic features of secondary infection No mycobacteria or parasites were detected
Fiber/foreign material composition via scanning electron microscopy with energy dispersive X-ray analysis and infrared spectroscopy	Birefringent material detected in 43% of biopsied lesions with most materials consistent with cellulose Material was in superficial scale crust, at the edge, or on the surface of the biopsy in 95% of biopsied lesions Two biopsies had evidence of foreign-body-type giant cells in response to cellulose consistent with cotton fiber in one and silicone in the other, both with features indicative of previous trauma

	Materials collected from non-lesional biopsies (23 fiber specimens from 12 patients) largely contained protein (83%) such as skin or cellulose (43%) such as cotton
Battery of laboratory blood tests	Most abnormalities reflected known comorbid conditions for specific patients Of 40 tested patients, 12.5% had signs of inflammation such as elevated rheumatoid factor or erythrocyte sedimentation rate, 10% had elevated antinuclear antibody, and 7.5% had elevated C-reactive protein
Serum test for <i>Borrelia burgdorferi</i> via polyvalent enzyme immunoassay and western blot, <i>Toxocara</i> via enzyme immunoassay, and <i>Strongyloides</i> via quantitative enzyme-linked immunosorbent assay	One borderline positive enzyme immunoassay for <i>Borrelia burgdorferi</i> No cases of positive immunoglobulin G for <i>Borrelia burgdorferi</i> detected by western blot Positive for <i>Toxocara</i> in three cases Positive for <i>Strongyloides</i> in three cases
Hair samples assessing for drug traces	Detection of one or more drugs in 20/40 patients: most commonly opiates and benzodiazepines with eight cases each, seven cases of cannabinoids, three cases of amphetamines, two cases of cocaine, and one case each of barbiturates and propoxyphene

Table 2. Summary and critique of publications supporting a psychiatric etiology of Morgellons disease. All studies have a level of “4” according to the Oxford Centre for Evidence-Based Medicine Levels of Evidence system [13].

Study	Relevant findings	Critiques
Hylwa, Bury, Davis et al. [15]	Of 108 delusional infestation patients diagnosed at Mayo Clinic who underwent skin biopsy and/or brought specimens to their physicians, 34 believed their infestation was due to fibers, specks, or grainy material. Histological examination of biopsies from all patients revealed no evidence of infestation as determined by pathologists independently of their clinical presentations. Bacteria were found in 25% of cultured skin biopsies	Only 31% of included patients reported infestation with a material that met Morgellons disease definition Biopsy culture results were not stratified by infesting agent (e.g. insects vs worms vs fibers) Bacterial species present in cultures were not specified Serological and PCR testing for <i>Borrelia burgdorferi</i> was not completed
Pearson, Selby, Katz et al. [13]	See Table 1	All patients were members of one healthcare plan in one region of the United States Relationships between cognitive deficits, drug detection, and other somatic complaints are correlative Use of positive and negative controls for serological testing was not reported PCR was not utilized on samples unless a pathogen was detected by tissue staining
Foster, Hylwa, Bury et al. [16]	Of 143 delusional infestation patients diagnosed at Mayo Clinic, there were 63 complaints of infestation with fibers, fuzz, black or white specks, white hair, black curls, and/or grainy material. A history of psychiatric illness was reported in 81% of all patients—most commonly depression, substance abuse, and anxiety. A past history of illicit drug use was reported in 22 patients. Active substance abuse was detected in six patients	Only a fraction of included patients reported infestation with a material that met Morgellons disease definition Relationships between psychiatric conditions and substance abuse are correlative Rates of comorbidities were not stratified by infesting agent (e.g. insects versus worms versus fibers) Serological testing and PCRs for <i>Borrelia burgdorferi</i> were not performed
Roncati, Gatti, Pusioli et al. [17]	Fibers from a Morgellons disease patient “without a rise” in <i>Borrelia burgdorferi</i> serology were analyzed by a field emission gun-environmental electron scanning microscope equipped with an X-ray microprobe. Fibers were identified as organic pet and human hairs and inorganic plastic fibers mimicking those found in the washing machine filter and indoor air in the patient’s apartment	Case study Method of <i>Borrelia burgdorferi</i> serology testing was not reported [3] Results of serology reported with ambiguous terminology No blinded electron scanning microscopy discrimination of patient fibers, human hair, and pet hair to support composition claim
Ohn, Park, Moon et al. [18]	Skin biopsy from a patient with belief of fiber infestation and black, brown, and red fibers visible with magnification under unbroken skin revealed a fiber extruding from the dermal side. Histologic evaluation, including with Warthin-Starry stain, did not show any microorganisms. Tissue culture was negative. Serology for <i>B burgdorferi</i> was negative. Filaments stained positively for keratin and negatively for collagen	Case study Lack of congruency between abstract and text body on type of testing for <i>Borrelia burgdorferi</i> completed (PCR vs serology) [3]
Yu, Ohn & Kim [10]	A patient with a belief of infestation with fiber-like materials and bugs was examined. Inorganic black fibers mixed with keratin were identified on dermoscopy. Histopathology of a lesion stained with periodic acid-Schiff and methenamine silver revealed no evidence of microorganisms. Serum PCR for <i>Borrelia burgdorferi</i> was negative	Case study Fiber composition was not evaluated Use of controls and blinding for PCR testing was not reported

<p>Mohandas, Bewley & Taylor [11]</p>	<p>Of 35 Morgellons disease patients seen in the Royal London Hospital psychodermatology clinic, 43% of patients had a diagnosis of depression, 26% had a diagnosis of anxiety, and 14% of patients had a history of substance misuse. <i>Borrelia</i> serology was positive in 0/10 tested patients</p>	<p>Included patients may overrepresent psychiatric comorbidities due to psychodermatologic nature of clinic Inclusion criteria were not reported Use of controls and blinding for serology were not reported</p>
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Table 3. Summary of publications supporting an infectious etiology of Morgellons disease and relevant critiques. All studies have a level of "4" according to the Oxford Centre for Evidence-Based Medicine Levels of Evidence system [13].

Study	Relevant findings	Critiques
Savely & Stricker [19]	Lyme disease was found in 97% of 122 Morgellons disease subjects by western blot (53%) or by meeting 5/7 clinical criteria (44%). Coinfections of <i>Borrelia burgdorferi</i> with <i>Babesia</i> species (18%) <i>Anaplasma phagocytophilum</i> (11%), <i>Ehrlichia chaffeensis</i> (10%), and <i>Bartonella henselae</i> (10%) were detected	Criteria for inclusion was identification of fibers by the first author alone Unspecified method of coinfection testing Use of negative controls and blinding not reported
Middelveen, Rasmussen, Kahn et al. [20]	Fibers from three Morgellons disease patients with history suggestive of <i>Borrelia burgdorferi</i> infection were structurally dissimilar to manufactured textiles on microscopy. Some fibers had bulbs suggesting modified hairs. Patient fibers resembled human hair when exposed to NaOH 10% and KOH 10% but were less resistant to NaOCl 12%. Patient fibers were less resistant to dissolution than bovine digital dermatitis fibers in all three solutions. Fibers immunostained for keratin	Small sample size (n=3) Subject selection process not provided Two selected cases had previous positive <i>Borrelia burgdorferi</i> serology and one had a previous tick-bite with bulls-eye rash Several samples of filaments were not attached to epithelial tissue No blinded microscopic differentiation of "modified hairs" and normal hairs No report of controls and blinding for chemical and immunostaining tests
Middelveen, Mayne, Kahn et al. [21]	Fibers from four Morgellons disease cases with positive <i>Borrelia burgdorferi</i> serology were hair-like in structure with a cortex surrounding a hollow medulla and protruded from the external surface of callus on microscopy. Staining revealed primarily collagen composition with patchy keratin. Fibers were associated with fibroblasts. Melanin was found in blue fibers. Spirochetes were detected by Warthin-Starry staining in two patients. A minority of colored fibers were identified as true hairs due to exclusive keratin composition. No hair-like scaling of the filaments was seen on scanning electron microscopy	Small sample size (n=4) Two of the cases were previously published at which time known positive testing for <i>Borrelia burgdorferi</i> years prior was reported [20] No report of negative control tissue specimens and blinding procedures for microscopy No blinded discrimination between the "modified hairs" and normal hairs Controls and blinding for immunostaining not reported
Middelveen, Burugu, Poruri et al. [22]	Four Morgellons disease cases with visible filaments and positive <i>Borrelia burgdorferi</i> serological testing were identified. Two had a history of treated Lyme disease. Calluses showed white, red, and blue filaments on light microscopy. Silver nitrate staining was positive for spirochetes in all patients. Immunofluorescence assay with <i>Borrelia</i> antibodies was positive in histological sections compared to a negative control of <i>Treponema denticola</i> spirochetes. PCR was positive for <i>Borrelia burgdorferi</i> in two patients and weakly positive in one relative to positive and negative controls	Sample size of four Two cases previously presented in Reference 20; all cases previously presented in Reference 21 reporting positive serology for <i>Borrelia burgdorferi</i> No negative control tissue specimens for microscopy Conflicting descriptions of negative controls for immunofluorescent light microscopy Controls used for PCR were not specified Blinding procedure for immunofluorescent assay and PCR testing not reported
Mayne [23]	Prevalence of Morgellons disease was 6% in a group of 500 seropositive Lyme patients.	Prevalence in population without Lyme Disease was not determined
Middelveen, Bandoski, Burke et al. [24]	25 Morgellons disease patients were included as subjects. 18/20 tested samples were positive for various <i>Borrelia</i> species DNA by PCR. 5/8 blood samples from PCR positive patients demonstrated bacteria consistent with <i>Borrelia</i> indicative of systemic infection. 19/19 tested samples were positive for <i>Borrelia burgdorferi</i> in-situ DNA hybridization with one or more probes. Collectively, 24/25 patients demonstrated molecular evidence of <i>Borrelia</i> by PCR	Five patients were presented in previous publications—four of which had previously known positive serology, anti- <i>Borrelia</i> immunostaining, and positive silver staining results while one had characteristic bulls-eye rash after a tick bite [20,21,22] No explanation for failure to perform all testing procedures on all samples

	and/or in-situ DNA hybridization. All laboratory studies were blinded and utilized positive and negative controls	
Fesler, Middelveen & Stricker [25]	Prevalence of Morgellons disease as classified by presence of microscopic fibers was 6% in a group of 1000 seropositive Lyme Disease patients. All of the Morgellons disease patients from this cohort were serologically positive for <i>Borrelia burgdorferi</i> . 77% of the Morgellons patients had serological evidence of coinfection with other tick-borne organisms such as <i>Bartonella</i> (25%), <i>Rickettsia</i> (25%), <i>Ehrlichia</i> (15%), and <i>Anaplasma</i> (10%) and/or with <i>Heliobacter pylori</i> (12%)	All patients were recruited from one undisclosed medical practice specializing in tickborne illnesses in San Francisco, California—the location of Stricker’s practice Morgellons disease patients were selected from a Lyme Disease population Use of controls and blinding for serological testing were not reported
Middelveen, Cruz, Fesler et al. [26]	Of 30 patients from across North America with embedded fibers as documented by healthcare professionals, 53% of patients were positive for <i>Borrelia burgdorferi</i> and/or relapsing fever <i>Borrelia</i> infection by PCR, and 63% were positive for one or both pathogens by western blot against positive and negative controls. More than >90% of patients were positive for <i>Borrelia burgdorferi</i> or relapsing fever <i>Borrelia</i> by western blot and/or PCR. <i>Bartonella henselae</i> was detected by PCR in 6/30 patients	Patients self-volunteered for this study advertising tick-borne disease detection and thus likely overrepresents exposure to tick-borne bacteria Use of controls for PCR testing was not reported Potential for false positive results ³¹
Middelveen, Filush, Bandoski et al. [27]	Blinded PCR detected <i>Borrelia burgdorferi</i> in 71% of lesions from 14 Morgellons patients and <i>Helicobacter pylori</i> in 86% of lesions. Positive and negative controls were used. All normal skin from healthy controls, Lyme patients, and Morgellons disease patients were negative for both pathogens	Patient selection process not reported Positive PCR for multiple organisms may reflect false-positive nonspecific results Association with <i>Borrelia burgdorferi</i> in Morgellons is less robust than <i>Helicobacter pylori</i> Cannot exclude secondary infection of lesion as all non-lesional skin was negative for microorganisms

Table 4. Summary of outcomes for treatment strategies used in delusions of parasitosis patients claiming infestation with fibers or other materials characteristic of Morgellons disease. All studies have a level of "4" according to the Oxford Centre for Evidence-Based Medicine Levels of Evidence system [13].

Study	Study design	Description	Primary outcome measure(s)	Results
Non-pharmacologic				
Gartner, Dolan, Stanford et al [36]	Case report	One patient treated with 6 one-hour hypnotherapy sessions occurring once a week	Patient distress and physical discomfort	Partial resolution with anxiety decreased by 75% and feelings of being bitten reduced by 57% at three-month follow-up
Comorbidity management and symptomatic treatment only				
Robles, Olson, Combs et al. [35]	Case series	Two patients treated with doxycycline 100mg twice daily for <i>Staphylococcus aureus</i> superinfection, hydrocolloid dressings, and frequent follow-up	Lesion status and persistence of fiber obsession	Full resolution in nine weeks
Mohandas, Bewley & Taylor [11]	Case series	Seven patients treated with combinations of citalopram 20mg daily or fluoxetine 40mg daily for comorbid psychiatric disorders with antibacterial emollients, minocycline 100mg daily, hydroxyzine 25mg nightly, zopiclone 7.5mg, and/or betamethasone solution	Lesion status and patient distress	Full resolution in one of seven patients; six of seven patients achieved at least partial resolution and were under review at time of publication
Alfaris, France, Sollecito et al. [37]	Case report	Patient reporting a fiber in the oral labial mucosa treated with topical clindamycin 1%, topical doxepin 5%, and mandibular soft splint to prevent biting	Lesion status	Full resolution in one year
First-generation antipsychotics				
Reid & Lio [4]	Case report	One patient treated with pimozide 2mg twice daily after failed antibiotics and topical medications	Lesion status	Full resolution in two months
Yan & Jorizzo [5]	Case series	Twenty-four patients treated with trifluoperazine 1-3mg daily	Lesion status and patient distress	29% reached full resolution (>90% clearance + no distress) on average of 2.3mg daily; 63% reached at least partial resolution (50-90% clearance and decreased distress) on average of 1.9mg daily
Second-generation antipsychotics				
Freudenreich, Kontos, Tranulis et al. [6]	Case report	One patient treated first with risperidone 2mg daily and later with aripiprazole 5mg	Persistence of fiber belief and pruritus	Partial resolution of belief on risperidone within weeks; full resolution of pruritus on aripiprazole
Dewan, Miller, Musters et al. [7]	Case report	One patient treated with trials of risperidone 0.5-2mg daily and olanzapine 5mg daily followed by olanzapine 2.5mg daily + ultraviolet light	Lesion status	No response to risperidone or olanzapine; partial resolution in three months on olanzapine + ultraviolet light
Mortillaro, Rodgman, Kinzie et al. [8]	Case report	One patient treated with lurasidone 20-80mg twice daily	Patient distress	Partial resolution

Ranka, Godse, Nadkarni et al. [9]	Case report	One patient treated with risperidone 2mg daily increased to twice daily with olanzapine 0.5mg daily and placebo emollient	Persistence of fiber belief and pruritus	Partial resolution (75% improvement) after 17 days of treatment
Yu, Ohn & Kim [10]	Case report	One patient treated with aripiprazole and fexofenadine (dosages not given) after failed ivermectin trials	Persistence of fiber belief and pruritus	Full resolution in two weeks
Mohandas, Bewley & Taylor [11]	Case series	Twenty-six patients treated with trials of second-generation antipsychotics: 18 trials of risperidone 0.5-2mg daily, 5 of quetiapine 100-400mg daily, 5 of olanzapine 2.5-15mg daily, 4 of amisulpride 50mg daily, and 1 of aripiprazole 5mg daily	New lesion incidence and patient distress	53.8% of patients on second-generation antipsychotics achieved near full resolution. 46.2% of patients achieved at least partial resolution and were under review at time of publication