LITERATURE REVIEW ON DEPRESSIVE SYMPTOMS IN PATIENTS WITH SARCOIDOSIS

Bachelor thesis Psychology and Health

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Tilburg, 2009-2010

Abstract

Purpose of review

The aim of this literature review was to provide information on depressive symptoms in patients with sarcoidosis. Therefore, data on prevalence, diagnosis, and treatment of depressive symptoms in sarcoidosis were analyzed.

Recent findings

Prevalences of depressive symptoms in patients suffering from sarcoidosis varied between 17% and 66%. Studies conducted in the United Stated found higher prevalences of depression than studies conducted in Europe. There were also differences between studies in the USA and Europe in the assessment instruments used to assess depressive symptoms. Several studies found that depression in patients suffering from sarcoidosis was associated with reduced quality of life.

Summary

Results from previous research showed that depressive symptoms are an important issue in patients with sarcoidosis. Patients suffering from sarcoidosis showed higher rates of depression than the general population. Different prevalences of depressive symptoms in sarcoidosis patients, varying between 17% and 66%, may be explained by the use of different assessment instruments for depressive symptoms. For example, the CES-D questionnaire, mainly used in the USA, seemed to find much higher prevalences than the BDI questionnaire, which is used in Europe. Moreover, the different prevalences of depressive symptoms in patients suffering from sarcoidosis may be attributed to different patient populations examined in the studies. More research is needed.

Keywords

Sarcoidosis, depressive symptoms, depression, quality of life, prevalence of depression, depression questionnaires.

Contents

Depressive symptoms in patients suffering from sarcoidosis

Sarcoidosis

Sarcoidosis is an inflammatory disease of unknown origin and is characterized by the presence of abnormal collections of inflammatory cells (granulomas). Almost every organ can be involved. However, granulomas most often appear in the lungs, the lymph nodes, the skin, and the eyes. Also the central nervous system, the heart, the liver and joints and muscles are frequently involved (Iannuzzi, Rybicki, & Teirstein, 2007; Newman, Rose, & Maier, 1997). Sarcoidosis occurs at all ages, with a peak incidence between 20 to 39 years. The peak incidence of sarcoidosis in African Americans occurs later in life, in the fourth decade. Iannuzzi et al. (2007) showed that sarcoidosis affects people of all races and from all ethnic groups, and the incidence of sarcoidosis varies throughout the world.

As previously mentioned, the clinical manifestations of sarcoidosis can involve only one organ system or may be widespread. Depending on the organ systems involved, symptoms can vary considerably. The majority of patients have constitutional symptoms such as fatigue, weight loss, fever and anorexia. Many of them also report respiratory symptoms such as dyspnea on exertion, cough and chest pain. In approximately 25 percent of patients, skin manifestations and ophthalmic lesions are reported (Newman et al., 1997; Wirnsberger et al., 1998b). Nonspecific symptoms, such as fatigue and sleeping disorders, cause the greatest impact on patients suffering from sarcoidosis (Wirnsberger et al., 1998a).

Psychological problems, such as depression and anxiety, are also common in patients suffering from sarcoidosis. Mental and emotional health concerns of patients with sarcoidosis appeared to be as important as physical complaints to patients' perceived wellbeing (Cox, Donohue, Brown, Kataria, & Judson, 2004). The impact of sarcoidosis is related to the severity of granulomatous inflammation and its effect on the function of vital organs (Newman et al., 1997). Drent et al. (1998) found that patients with physical complaints were more likely to be depressed than those without complaints. In conclusion, depressive symptoms are an important issue in sarcoidosis.

Depressive Symptoms

The prevalence of depressive disorders is high in patients with medical illness, especially in chronic medical disorders. Comorbidity with depressive symptoms and chronic medical illness is often associated with amplification of chronic medical illness symptoms and increased symptom reporting. Multiple studies have shown that major depression in patients

with chronic medical illness leads to additive function impairment, increased symptom burden, impaired self-care and adherence, and increased medical costs (Katon & Ciechanowski, 2002). Major depression is also associated with decreased quality of life (Katon, 2003).

Key features of depressive disorder are depressed mood and loss of interest or pleasure in most activities (Cassano & Fava, 2002). According to the Diagnostic and Statistical Manual of Mental Disorders (4th ed., text rev.; *DSM-IV-TR*; American Psychiatric Association, 2000), a person who suffers from major depressive disorder must either have a depressed mood or a loss of interest or pleasure in daily activities for at least a two week period. Furthermore, the *DSM-IV-TR* (2000) considers that depressive symptoms due to medical illness should be excluded to make the diagnosis of major depressive disorder. Nevertheless, depressive disorders are frequently associated with medical illness. Therefore, clinicians ignore this hierarchical approach and diagnose major depressive disorder even when a comorbid medical condition is present.

Sarcoidosis and depression can influence each other. Depression significantly influences the course of concomitant medical illnesses (Cassano & Fava, 2002). Furthermore, depression causes additive functional impairment in medical disorders (Katon & Ciechanowski, 2002). Simultaneously, previous studies have shown that as the number of medical symptoms increased, so did the percentage of depressive disorders. Also, chronic pain may provoke depressive disorder (Katon, 2003). Often there is an overlap between symptoms of the somatic illness and those considered indicative of depression (Van Ede & Yzermans, 1999). However, depression is treatable and treatment may improve mood and reduce somatic complaints (Ruttley & Reid, 2006). Therefore, it is important to study sarcoidosis and depressive symptoms.

Study Aim

The aim of this study is to review the literature about depressive symptoms in patients suffering from sarcoidosis. Therefore, data on prevalence, diagnosis, and treatment of depressive symptoms in sarcoidosis are analyzed.

This review was conducted to answer the following questions:

- What is the prevalence of depressive symptoms in patients suffering from sarcoidosis?
- Which methods are used to assess depressive symptoms in patients suffering from sarcoidosis?

- What is the impact of depressive symptoms on patient's quality of life?
- Is treating depressive symptoms useful for the course and prognosis of sarcoidosis?

It is important to analyze diagnosis and treatment of depressive symptoms in patients with sarcoidosis, because treating depressive symptoms in sarcoidosis patients may improve their quality of life and the course of the disease. This review will outline the current state of research on depressive symptoms in patients with sarcoidosis.

Methods

Literature Search

A computerized search of the literature was performed, using Science Direct, PubMed, Web of Science and PsychINFO databases. The databases were searched for the period from 1980 until August 2009. First, a search was performed with Science Direct, using the key words 'sarcoidosis and depression' and 'sarcoidosis and depressive symptoms'. The results were limited to journals. This resulted in 1799 and 92 hits, respectively. Five articles found with the key words 'sarcoidosis and depressive symptoms' overlapped the other search. Furthermore, a search with the same keywords was performed with PubMed. Because the results of 'sarcoidosis and depressive symptoms' were the same as 'sarcoidosis and depression', only the last one will be discussed. This search resulted in 76 hits. Three of the articles found overlapped the previous searches. Finally, Web of Science and PsychINFO were searched using the key words 'sarcoidosis and depression'. This resulted in 39 and 11 hits, respectively. Of the articles found in Web of Science, thirteen overlapped with previous searches, in PsychInfo just two overlapped. In total, 2017 potentially relevant articles were identified.

Selection Criteria

After identifying the potentially relevant articles, they were selected based on the following selection criteria:

- Study objective is to describe depressive symptoms or depression in sarcoidosis.
- Study population consists only of patients suffering from sarcoidosis.
- A specific depression questionnaire is used.
- The article is published in English.

- The article is a full report.

These selection criteria were applied to the 2017 potentially relevant articles. After inspecting the titles and abstracts, 19 articles met the criteria and were selected. After checking the references of all selected articles, one article was selected as well. Because there was no full text of two articles on the internet, these articles were obtained from the authors.

Twenty articles seemed to fulfil the selection criteria and of these articles the full publications were retrieved. After detailed evaluation of the remaining articles, nine articles were excluded because they did not fulfil the selection criteria. Finally, 11 articles were included in the review (Antoniou et al., 2006; Chang et al., 2001; Cox et al., 2004; De Vries & Drent, 2004; Drent et al., 1998; Goracci et al., 2008; Klonoff & Kleinhenz, 1993; Spruit et al., 2004; Wirnsberger et al., 1998a; Wirnsberger et al., 1998a; Yeager et al., 2005). Figure 1 shows the flow chart of the study selection.

Quality Assessment

After including the articles, the methodological quality of each article was assessed. Therefore, a list of 15 standardized predefined criteria was used. This checklist is a modified version of an established criteria list for systematic reviews and was largely based on De Kleijn et al. (2009) and Mols, Vingerhoets, Coebergh, & Van de Poll-Franse (2005). The criteria are showed in table 1.

Aspects of the selected articles that met a criterion, were assigned one point. No point was assigned when an aspect did not meet a specific criterion or when it was described insufficiently or not at all (De Kleijn et al., 2009; Mols et al., 2005).

If studies met all criteria, they had the highest possible score of 15 points. Studies scoring 75% or more of the maximum attainable score (>11 points) were supposed to be of high quality. Studies scoring between 50% and 75% (8-11 points) were of moderate quality and studies scoring lower than 50% (<8 points) were considered low quality (Mols et al., 2005).

Results

Quality Assessment

The full quality assessment of the articles included in this review is showed in table 2. This review contains of two studies of high quality. Seven studies were of moderate quality and two were of low quality. Because of the low number of selected articles, studies of low

quality were also included in this review. These low quality studies were valued as less important than articles of high or moderate methodological quality.

Though, there seems to be no relationship between the quality of the studies and the reported prevalences of depressive symptoms and assessment instruments for depressive symptoms. For instance, the two studies of high quality included in this review found prevalences of 66% and 18%.

Study Characteristics

Eleven studies were included in this review, all published after 1992. Four studies were conducted in the USA (Chang et al., 2001; Cox et al., 2004; Klonoff & Kleinhenz, 1993; Yeager et al., 2005), four in the Netherlands (De Vries & Drent, 2004; Drent et al., 1998; Wirnsberger et al., 1998a; Wirnsberger et al., 1998b) and one in Belgium (Spruit et al., 2005), Italy (Goracci et al., 2008) and Greece (Antoniou et al., 2006). The main findings are showed in table 3. Depression or depressive symptoms were not the major outcome in all studies, however, all studies reported a prevalence of depression.

Five studies evaluated quality of life and mental health in patients suffering from sarcoidosis (Antoniou et al., 2006; Cox et al., 2004; Drent et al., 1998; Goracci et al., 2008: & Wirnsberger et al., 1998a). Furthermore, two studies compared psychosocial factors and scores on psychological tests with results from pulmonary function tests (Klonoff & Kleinhenz, 1993; Yeager et al., 2005). Another study examined sociodemographic and disease morbidity factors associated with depression in patients suffering from sarcoidosis (Chang et al., 2001). Spruit et al. (2005) investigated the relationship between skeletal muscle weakness and reduced health status and De Vries & Drent (2004) examined the role of perceived stress in sarcoidosis. Finally, one study made an inventory of the clinical presentation of the sarcoidosis population in the Netherlands (Wirnsberger et al., 1998b).

In the following paragraphs the different research questions will be discussed. First, the prevalence of depressive symptoms will be analyzed. Subsequently, different assessment instruments for depressive symptoms will be reviewed. Finally, the impact of depressive symptoms on quality of life of patients suffering from sarcoidosis will be discussed. Since there was no available information about treating depressive symptoms for the course and prognosis of sarcoidosis, there is no paragraph concerning this question.

Prevalence of Depressive Symptoms in Patients Suffering from Sarcoidosis

All studies recognized that depression and depressive symptoms were very important issues for sarcoidosis patients. However, they found different prevalences of depressive symptoms. The highest prevalences of depression were 60% and 66%, found by Chang et al. (2001) and Cox et al. (2004), respectively. Three studies conducted in the Netherlands found the lowest prevalences of depression: 18%, 18% and 17% (Drent et al., 1998; Wirnsberger et al., 1998a; Wirnsberger et al., 1998b). Goracci et al. (2008) also found a rather low prevalence of depression: 25%. Two other studies found middle ranged prevalences of depression: Spruit et al. (2005) found a prevalence of 38% and Yeager et al. (2005) a prevalence of 46%.

Some studies did not report a prevalence of depressive symptoms, only the mean and standard deviation (x±SD) of the scores on the assessment instruments for depression. Antoniou et al. (2006) used the Hospital Anxiety and Depression scale and they reported a mean depression score of 4.9±5 (n=75). The mean depression score of 30 healthy controls was 2.4±0.4. The scores ranged from 0 to 21. A score between 8 and 10 is suggestive of depression and a score of >10 indicates depression. These depression scores suggested that sarcoidosis patients scored significantly higher on depressive symptoms than healthy controls (p=0.007), but they did not meet the criteria for depression (Antoniou et al., 2006). Klonoff & Kleinhenz (1993) and De Vries & Drent (2004) used the Beck Depression Inventory to assess depression. They reported mean depression scores of 11.82±8.52 and 10.2±6.4, respectively. The cut-off point for the diagnosis of major depression was 21 in both studies. De Vries & Drent (2004) also reported a range of 0-41. This suggested that at least some sarcoidosis patients met the criteria for clinical depression. Sarcoidosis patients, as a group, did not meet the criteria for clinical depression.

Some studies reported not only prevalences of depressive symptoms, but also gave more information about depressive symptoms in patients suffering from sarcoidosis. For example, Drent et al. (1998) and Wirnsberger et al. (1998a) found that respondents with actual complaints were more likely to be depressed than respondents without complaints. They had significantly higher BDI-scores and more depressive symptoms. Moreover, female sex, decreased access to medical care, and increased dyspnea on exertion all predicted depression (Chang et al., 2001). Chang et al. (2001) also found that as more organ systems were involved in sarcoidosis, the prevalence of depressive symptoms increased. De Vries & Drent (2004) found that having psychological problems, such as depression, was related to patient's perception of future symptom development. Patients who thought that their symptoms would diminish had higher scores on the BDI than other patients. Moreover, they reported having

psychological problems. De Vries & Drent (2004) also found that perceived stress was correlated with the BDI. Male patients showed stronger relationships between perceived stress and depression than female patients. Klonoff & Kleinhenz (1993) reported that sarcoidosis patients may show a more general pattern of emotional distress rather than a specific psychological disorder (e.g., depression). Furthermore, Antoniou et al. (2006) found no correlation between duration of disease, quality of wellbeing and anxiety and depression scales. At last, Yeager et al. (2005) found that a greater degree of shortness of breath was associated with an increased Body Mass Index and depression score.

Methods to Diagnose Depressive Symptoms in Patients Suffering from Sarcoidosis

The eleven analyzed studies used different instruments to measure depressive symptoms. Most studies used standardized questionnaires. One used a questionnaire that was not standardized (Wirnsberger et al., 1998b).

The most frequently used assessment scale of depression was the Beck Depression Inventory (BDI). This questionnaire was used by De Vries & Drent (2004), Drent et al. (1998), Klonoff & Kleinhenz (1993) and Wirnsberger et al. (1998a). The BDI is a well validated instrument that correlates well with diagnostic criteria. This instrument takes 5-10 minutes to complete and it consists of 21 statements which are grouped in 21 groups of four possible responses. The respondent was asked to select one statement from each group. Each answer was scored on a four-point Likert-type scale ranging from 0-3. The total score indicates the severity of depression (Beck, Steer, & Garbin, 1988). Drent et al. (1998) and Wirnsberger et al. (1998a) considered patients with a total score of 15 or above to have significant depressive symptoms. De Vries & Drent (2004) and Klonoff & Kleinhenz (1993) used a cut-off score of 21. Originally, various cut-off score ranges for the BDI were used. A cut-off score of <10 was considered to be none ore minimal depression. Furthermore, a cut-off score of 10-18 indicates mild to moderate depression, 19-29 indicates moderate to severe depression and 30-63 indicates severe depression (Beck, Steer, & Garbin, 1988). The BDI can be separated into a Physical Depression Index (PDI) and a Cognitive Depression Index (CDI). The Physical Depression Index is used to control the physical effects of the illness on mood. The remaining items are called the Cognitive Depression Index. The CDI might be a better predictor of depression in medical patients because it shows less confusion caused by symptoms of physical illness that are similar to symptoms of depression (Drent et al., 1998; Wirnsberger et al., 1998a). The four studies that used the BDI to measure depression had low prevalences of depression. Two of them were of moderate quality and two of high quality.

Chang et al. (2001), Cox et al. (2004) and Yeager et al. (2005) used the Center for Epidemiologic Studies – Depression Scale (CES-D). The CES-D scale is a simple self-report measure that has been validated for use in general population (Radloff, 1977). In all studies the shortened 11-item version was used. In the shortened 11-item version, a cut-off score of ≥9 was used to indicate depression. The CES-D consists of 11 items; respondents rate the frequency of symptoms in the last week on a four-point scale from "rarely" to "most of the time" (Chang et al., 2001). Two studies of high quality and one of moderate quality used the CES-D to measure depression. These three studies had the highest prevalences of depression (Chang et al., 2001; Cox et al., 2004).

The Hospital Anxiety and Depression Scale (HADS) was used by Antoniou et al. (2006) and Spruit et al. (2005). The HADS is a domain specific questionnaire to assess mood state. It consists of 14 statements: seven reflecting anxiety and seven reflecting depression. Each item on the depression scale has to be answered by the respondent on a four point scale of 0-3, the scores ranging from 0 to 21 (Spinhoven et al., 1997). Both studies used a cut-off score of 10. A total score of 10 or higher indicates probable presence of depression, while a score below 8 indicates no evidence of depression. A score between 8 and 10 is suggestive of depression (Antoniou et al., 2006; Snaith, 2003). The two studies had a moderate quality. Spruit et al. (2005) found a prevalence of depressive symptoms of 38% and Antoniou et al. (2006) reported that sarcoidosis patients score slightly higher on depressive symptoms than controls and that they do not meet the criteria for depression

The MINI-PLUS was used by Goracci et al. (2008). They also used a DSM-IV axis I diagnosis. This study did not give additional information about the assessment instrument. The MINI is a short, structured diagnostic interview, developed for DSM-IV and ICD-10 psychiatric disorders. The MINI-PLUS is an extended version of the MINI, designed for research, with a duration of 45-60 minutes. The MINI-PLUS includes 23 disorders. Interrater agreement between MINI diagnoses from general practitioners and psychiatrists was found in 85% of the cases, with the highest agreement for major depressive disorder (Sheehan et al., 1998). This study of Goracci et al. (2008) had a moderate quality and a prevalence of depressive symptoms of 25%.

Impact of Depressive Symptoms on Quality of Life of Patients Suffering from Sarcoidosis

Depressive symptoms can have a considerable impact on quality of life of patients suffering from sarcoidosis. Unfortunately, only two studies were found regarding the impact of depressive symptoms on quality of life of sarcoidosis patients.

Goracci et al. (2008) confirmed the high rate of comorbid psychiatric disorders in patients suffering from sarcoidosis and its relationship with a poorer quality of life. Sarcoidosis patients with a comorbid psychiatric disorder had a poorer quality of life, especially on the domains physical health/activities, leisure time activities, general activities and feelings of the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q).

Moreover, psychological health and depressive symptoms were associated in patients suffering from sarcoidosis (Wirnsberger et al., 1998a). Wirnsberger et al. (1998a) suggest that treating depressive symptoms may improve quality of life in these patients.

Discussion

The purpose of this review was to outline the current state of research on depressive symptoms in patients suffering from sarcoidosis. Conclusions from previous research about depressive symptoms in sarcoidosis patients will be summarized and analyzed.

Prevalence of Depressive Symptoms

Previous research on depressive symptoms in patients with sarcoidosis found different prevalences of depressive symptoms, varying between 17% and 66%. The three highest prevalences of depressive symptoms were found by studies conducted in the USA (Chang et al., 2001; Cox et al., 2004; Yeager et al., 2005). One study was of high quality (Cox et al., 2004) and two were of moderate quality (Chang et al., 2001; Yeager et al., 2005). The lowest prevalences were found by three studies conducted in the Netherlands (Drent et al., 1998; Wirnsberger et al., 1998a; Wirnsberger et al., 1998b). The quality of these studies varied: one was of high quality (Drent et al., 1998), one of moderate quality (Wirnsberger et al., 1998a), and one of low quality (Wirnsberger et al., 1998b). Moreover, two studies found prevalences of 25% and 38% (Goracci et al., 2008; Spruit et al., 2005). Both studies were of moderate quality. The three remaining studies did not report prevalences of depressive symptoms, only the mean and standard deviation (x±SD) of the scores on the assessment instruments for

depression. The studies of Antoniou et al. (2006) and De Vries & Drent (2004) were of moderate quality and the study of Klonoff & Kleinhenz (1993) was of low quality.

The considerable differences in prevalences of depressive symptoms found in these studies may be ascribed to the questionnaires used. For example, the three studies that found the highest prevalences of depressive symptoms all used the CES-D, and two of the studies that found the lowest prevalences used the BDI questionnaire. The CES-D questionnaire may be more sensitive for depression than the BDI questionnaire. Accordingly, in the same patient population, the CES-D will give a higher prevalence of depression. Furthermore, the BDI consists of 21 items and the CES-D consists of 11 items. This considerable difference may indicate that the BDI is more accurate than the CES-D, as a result of the higher number of items. This suggests that the lower prevalences of depressive symptoms found by studies using the BDI may be more reliable.

Furthermore, the differences in prevalences of depressive symptoms may also be attributed to the country in which the study was conducted. For example, studies conducted in the USA found much higher prevalences of depressive symptoms in patients suffering from sarcoidosis than studies conducted in the Netherlands.

There are several explanations for these differences. First, there are differences in population between the USA and the Netherlands. For instance, studies conducted in the USA regularly include a high percentage of African Americans, whereas studies conducted in Europe mainly include white subjects. In their Statement on Sarcoidosis, the American Thoracic Society (1999) point out that the lifetime risk of sarcoidosis is 0.85% for US whites and 2.4% for US blacks. The American Thoracic Society (1999) also remark that sarcoidosis in black people is more severe than in white people, who are more likely to present with asymptomatic disease. There might be a relationship between severity of sarcoidosis and depressive symptoms. The high prevalences of depressive symptoms in the USA may be attributed to the high percentage of African Americans, since they have a considerable higher risk for sarcoidosis and their sarcoidosis is more severe than in whites.

Furthermore, literature shows that ethnic and racial minorities do not have the same access to medical care as the majority white population (Mayberry, Mili, & Ofili, 2000). This is particularly true for African Americans. Mayberry and colleagues (2000) also state that the impact of these differences is related to socioeconomic and insurance status. Access to medical care and socioeconomic status have been associated with depressive symptoms in patients with chronic diseases (Curtis & Borson, 2001).

Moreover, there seems to be no relationship between the quality of the studies and the reported prevalences of depressive symptoms. For instance, the two studies of high quality included in this review found prevalences of 66% and 18%. Overall, literature shows that psychological problems such as feeling depressed are an important issue for patients suffering from sarcoidosis. Nevertheless, physicians may underestimate the importance of problems related to sarcoidosis.

In conclusion, prevalences of depression can vary considerably. Prevalences found in the USA seem to be higher than prevalences found in Europe. However, depression is an important issue in sarcoidosis and needs further investigation.

Because there has not been much research on depressive symptoms in sarcoidosis patients, two more well-known comparable diseases in which depression is common will be discussed. For example, rheumatoid arthritis (RA) and sarcoidosis have several aspects in common. They both are inflammatory diseases of unknown cause and occur in relatively young people on a regular basis. The clinical course of sarcoidosis and RA is rather unpredictable, varying from a chronic course to spontaneous remission or, on the contrary, rapid progression. Although manifestations of RA are mainly in the joints, also systemic symptoms and extra-articular inflammation may be reported. Even pulmonary involvement in RA may occur occasionally. Patients with sarcoidosis and patients suffering from RA present the same aspecific symptoms, such as fatigue, arthralgia and muscle pain. Finally, no specific treatment is known for either of the disorders (Wirnsberger et al., 1999). There have been a few studies on RA and depression. The prevalence of depression in patients with RA has been found to be consistent with rates of depression among other chronic illnesses, between 12,5% and 25% (Murphy, Dickens, Creed, & Bernstein, 1999). These prevalences are slightly lower than the prevalences found in research on sarcoidosis. This difference may be ascribed to the place of the clinical manifestations. Sarcoidosis mainly affects the lungs, the lymph nodes, the skin, the eyes, and other organ systems, whereas RA generally affects the joints. This suggests that clinical manifestations in the lungs are experienced as more severe than clinical manifestations in the joints, and patients who are experiencing clinical manifestations in the lungs are more likely to have depressive symptoms.

Furthermore, sarcoidosis can be compared with chronic obstructive pulmonary disease (COPD). Sarcoidosis and COPD have some symptoms and consequences in common such as fatigue, reduced appetite, insomnia, reduced self esteem and social embarrassment because of the chronic cough (Goracci et al., 2008). In nearly all cases of sarcoidosis the lungs are involved. Most commonly are respiratory symptoms such as limitation in air flow, also very

often seen in COPD (Iannuzzi et al., 2007; Newman et al., 1997). Previous research on COPD and depression shows a higher prevalence of depression among COPD patients than among controls and the risk of depression is only increased in patients with severe airways obstruction (Van Ede & Yzermans, 1999; Van Manen et al., 2002). Furthermore, respiratory symptoms and physical impairment are related to depression in patients with COPD, which indicates that depression will also affect sarcoidosis patients (Van Manen et al., 2002). Research among patients with chronic cough showed an even higher prevalence of depression than in other chronic patient populations (Dicpinigaitis, Tso, & Banauch, 2006). Kunik et al. (2005) found a high prevalence of depression in patients with chronic breathing disorders, including COPD. In this study, Kunik and his colleagues found a prevalence of 80% screening positive for depression, anxiety or both. Of these patients, 65% screened positive for both anxiety and depression, 10% screened positive for anxiety and 5% screened positive for depression. This indicates a prevalence of depressive symptoms of 70%. This prevalence is considerably higher than the prevalences of depressive symptoms in sarcoidosis. This difference may also be ascribed to the place of the clinical manifestations. While COPD exclusively affects the lungs, sarcoidosis can affect different organ systems. Furthermore, sarcoidosis may affect only one organ system or may be widespread. There also may be a difference in the severity of the clinical manifestations. The quite high prevalence of depressive symptoms in COPD also suggests that clinical manifestations in the lungs are experienced as more severe than clinical manifestations in other organ systems. Goracci et al. (2008) showed that sarcoidosis patients with multi-systemic involvement endorse significantly worse quality of life than subjects with no multi-systemic involvement. Accordingly, Desbiens and his colleagues (1999) reported that patients with multiple organ system failure or metastatic lung cancer, among other diseases, had the greatest symptom burden. These patients also reported poorer quality of life. Furthermore, depression is one of the most common symptoms in sarcoidosis (Desbiens et al., 1999). This suggests a higher prevalence of depressive symptoms among sarcoidosis patients with multi-systemic involvement. However, Goracci et al. (2008) and Desbiens et al. (1999) did not investigate depressive symptoms. This subject needs further investigation.

In conclusion, the prevalences of depressive symptoms in patients suffering from sarcoidosis differ from literature about comparable medical illnesses. Prevalences of depressive symptoms in RA patients are slightly lower than prevalences of depressive symptoms in patients suffering from sarcoidosis. Moreover, prevalences of depressive symptoms in COPD patients are quite higher than in sarcoidosis patients. As mentioned

before, these differences might be explained by the place of clinical manifestations. Clinical manifestations in the lungs may be experienced as more severe than clinical manifestations in other organ systems. This suggests that patients who are experiencing clinical manifestations in the lungs are more likely to have depressive symptoms. These differences also might be explained by the use of different patients groups. All studies on depressive symptoms in sarcoidosis, RA, or COPD used different patient populations. For example, percentages of ethnic groups were different, as well as population sizes.

Differences in prevalences of depressive symptoms might also be explained by using different questionnaires. Research on depressive symptoms in COPD patients used the CES-D questionnaire and found high prevalences of depressive symptoms. Studies using the CES-D to asses depressive symptoms in patients suffering from sarcoidosis found high prevalences of depressive symptoms as well. Research on depressive symptoms in RA patients used the HADS questionnaire and found a quite low prevalence of depressive symptoms. On the contrary, studies using the HADS to asses depressive symptoms in sarcoidosis patients found a more moderate prevalence of depressive symptoms. This suggests that differences in prevalences of depressive symptoms not only may be explained by using different questionnaires. Other factors, such as the severity of the disease or the patient population, may also be important.

Methods to Diagnose Depressive Symptoms

The reviewed studies used four different instruments to assess depressive symptoms. Four studies used the Beck Depression Inventory (BDI). Three of these studies were conducted in the Netherlands and one was conducted in the USA. One study was of high quality (Drent et al., 1998) and two studies were of moderate quality (De Vries & Drent, 2004; Wirnsberger et al., 1998a). The study conducted in the USA was of low quality (Klonoff & Kleinhenz, 1993). Three studies used the Center for Epidemiologic Studies – Depression scale (CES-D). All three studies were conducted in the USA and showed high prevalences of depression. One of the studies was of high quality (Cox et al., 2004) and two were of moderate quality (Chang et al., 2001; Yeager et al., 2005). Two studies used the Hospital Anxiety and Depression Scale (HADS). These studies were conducted in Greece and Belgium and both studies were of moderate quality. Goracci et al. (2008) used the MINI-PLUS. This study was conducted in Italy and was of moderate quality.

In conclusion, the CES-D seems to be a typical American questionnaire. In Europe, the BDI, the HADS and the MINI-PLUS were used. Diverse questionnaires may lead to different

prevalences of depressive symptoms in the USA and in Europe. This subject needs further investigation. The questionnaire used and the methodological quality of the study were not related. For example, studies using the BDI were of high, moderate and low quality. The studies using the CES-D were of high and moderate quality and the studies using the HADS and MINI-PLUS were of moderate quality. This suggests that the methodological quality of the articles was not influenced by the questionnaires used. Differences in methodological quality may be ascribed to several other factors, such as study design or patient population.

In research on comparable medical illnesses such as RA and COPD, the same assessment instruments for depression are used. For example, Murphy et al. (1999) used the HADS to assess depression in patients with RA. They found the prevalences of depression to be consistent with rates of depression among other chronic illnesses. Kojima et al. (2009) used the BDI to assess depression and found that RA patients with severe pain had significantly higher scores on depression than RA patients without severe pain. Furthermore, Van Manen et al. (2002) used the CES-D to assess depression in patients with COPD. He found that respiratory symptoms in patients with COPD are related to depression. Dicpinigaitis, Tso, & Banauch (2006) also used the CES-D to assess depression. Dicpinigaitis and colleagues (2006) found that patients with chronic cough showed higher prevalences of depression than other chronic patient populations. Finally, Kunik et al. (2005) used the BDI and found high prevalences of depression in patients with COPD and other chronic breathing disorders.

The questionnaires used to assess depression in sarcoidosis, and comparable medical illnesses such as rheumatoid arthritis and chronic obstructive pulmonary disease, are largely the same. The fact that these questionnaires are widely used, for different illnessess and in different patient populations, suggests the questionnaires are of good methodological quality.

Quality of Life and Depressive Symptoms

Furthermore, the impact of depressive symptoms on patient's quality of life will be discussed. Only two articles were found regarding the impact of depressive symptoms on quality of life of patients suffering from sarcoidosis. Three studies showed that quality of life and depressive symptoms are related. Cox, Donohue, Brown, Kataria & Judson (2003) and Drent et al. (1998) found that health related quality of life is associated with depression in patients with sarcoidosis, even after controlling for demographical, medical and psychological variables. Furthermore, symptoms like fatigue and sleeping disorders have a great impact on both quality of life and depression. Clinical depression and depressed mood are known to be associated with a lowered quality of life (Wirnsberger et al., 1998a).

In conclusion, depressive symptoms and lowered quality of life both have a considerable impact on patients suffering from sarcoidosis. They also might influence each other.

Limitations

There are several limitations to this literature review. To start with, few articles were included in this literature review because there was not much research about depressive symptoms in patients suffering from sarcoidosis available yet. Among the selected articles there were only two of high methodological quality. Therefore, all studies of moderate and low quality were also included in this review. Although articles of low quality were valued as less important than articles of high and moderate quality, using these articles of low quality may affect the conclusions. Furthermore, because of the lack of articles, all relevant information from the included studies was used in this review. Therefore, conclusions may be drawn on the basis of one article.

There are also limitations to this field of research. For example, the studies included in this review examined different aspects of sarcoidosis, therefore it was difficult to compare literature. Likewise, the studies used different patient populations. For example, Cox et al. (2004) used 120 outpatients with sarcoidosis presenting to a university medical center outpatient pulmonary clinic. On the other hand, De Vries & Drent (2004) approached all members of the Dutch Sarcoidosis Society (DSS) and 1046 patients were included in their study. There are obvious differences between these two patient populations, which makes it difficult to compare these groups. Furthermore, patient populations differ on several clinical variables, such as stage of disease, definition of depression or depressive symptoms and treatment of sarcoidosis or depression. Finally, there was just one study that used a longitudinal design. Others used cross-sectional and case-control study designs. Therefore, it is difficult to study development of depression in sarcoidosis. Because of these limitations, it is difficult to draw conclusions. Accordingly, all conclusions must be interpreted carefully.

Conclusions

In conclusion, this literature review shows that depressive symptoms are an important issue in patients suffering from sarcoidosis. The studies included in this review show that the prevalence of depressive symptoms in sarcoidosis patients is higher than in general population, varying between 17% and 66%. Prevalences of depressive symptoms in the USA seem to be higher than in Europe. These differences need further investigation. Prevalences of

depressive symptoms in patients suffering from sarcoidosis are somewhat different from literature about depressive symptoms in comparable medical illnesses such as rheumatoid arthritis and chronic obstructive pulmonary disease. Prevalences of depressive symptoms in RA patients are slightly lower than in sarcoidosis patients. Prevalences in COPD patients are higher than in sarcoidosis patients.

Moreover, studies use different assessment instruments for depression, such as the BDI (mainly in Europe) and the CES-D (mainly in the USA), as well as the MINI-PLUS and the HADS. In literature on depressive symptoms in patients suffering from medical illnesses comparable to sarcoidosis, such as RA and COPD, the same questionnaires are used.

Furthermore, previous research found reduced quality of life in patients suffering from sarcoidosis. Literature also showed that quality of life is related with depressive symptoms.

One of the purposes of this review was to find out if treating depressive symptoms is useful for the course and prognosis of the disease. This is an important question, because treating depressive symptoms in patients suffering from sarcoidosis may improve their quality of life and their prognosis. Unfortunately, no studies have been conducted on this topic yet. For future research it is recommended to focus on the effect of treatment on depressive symptoms in patients suffering from sarcoidosis.

Quality assessments were made of all studies included in this review. Methodological quality of the study was not related to the prevalence of depressive symptoms reported or the questionnaires used. The quality assessments did not contribute to the clarification of the relationship between sarcoidosis and depression. More research is needed to explore this relationship.

Moreover, for future research it is recommended to accomplish more prospective follow-up studies focusing on depressive symptoms in sarcoidosis. Furthermore, an extensive international study may be useful for explaining differences between for instance the USA and the Netherlands. When using one assessment instrument, cultural differences will become more visible. For future research it is also recommended to use a control group; a comparison between depressive symptoms in general population and depressive symptoms in sarcoidosis patients is needed.

This literature review provides a summary and an evaluation of the research field on depressive symptoms in patients suffering from sarcoidosis until now. It makes the gaps in this area of research more visible and shows us that a lot of additional research is needed.

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Appendix

Figure 1

Study selection process

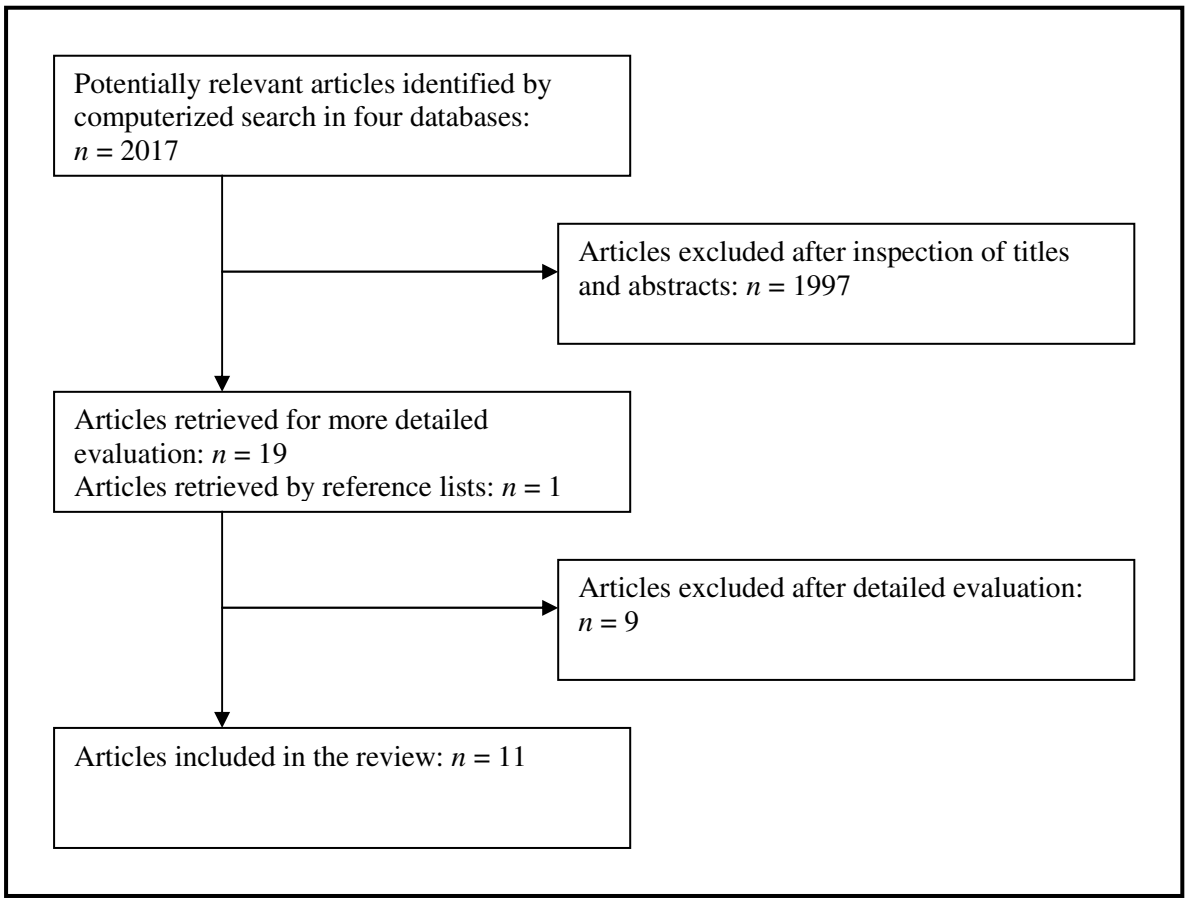

Table 1

Criteria list for assessing the methodological quality

	Criteria list for assessing the methodological quality of studies on depression in patients suffering from sarcoidosis. Positive if:
A	Sociodemographic variables are described (e.g., age, sex, race, employment status, educational status).
B	Clinical variables are described (e.g., duration of symptoms, use of medications, lung function tests).
C	Inclusion and/or exclusion criteria are specified.
D	The study population consists of at least 50 patients.
E	Diagnosis according to the WASOG-criteria.*
F	Definition of depression or depressive symptoms is present.
G	Patients signed an informed consent form before participating in the study.
H	Participation and response rates are described and above 75%.
I	Characteristics of responders are compared with non-responders in order to give information about the representativeness of the responders.
J	The process of data collection is described (e.g., self-report, interview).
K	A standardized or valid depression questionnaire is used.
L	The mean, median, standard deviations or percentages are reported for the most important outcome measures.
M	The study describes potential prognostic factors by using multivariate analysis or structural equation modeling.
N	The results are compared between two or more groups (e.g., healthy population, groups with different stages of sarcoidosis).
O	The design is longitudinal (more than 1 year).

* As mentioned in the Statement on sarcoidosis (American Thoracic Society, 1999).

Table 2

Methodological quality of studies on depression in patients suffering from sarcoidosis

Study	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	Quality score	Score (%)
Cox et al. (2004)	1	1	1	1	1	0	1	1	0	1	1	1	1	1	0	12	80%
Drent et al. (1998)	1	1	1	1	1	0	1	1	0	1	1	1	1	1	0	12	80%
Chang et al. (2001)	1	1	1	1	0	0	1	1	0	1	1	1	1	1	0	11	73%
Wirnsberger et al. (1998a)	1	1	1	1	1	0	1	1	0	1	1	1	0	1	0	11	73%
Antoniou et al. (2006)	1	1	1	1	1	0	1	1	0	1	1	1	0	1	0	11	73%
Goracci et al. (2008)	1	1	0	1	1	0	1	0	0	1	1	1	0	1	0	9	60%
Spruit et al. (2005)	1	1	1	0	1	0	1	1	0	0	1	1	0	1	0	9	60%
Yeager et al. (2005)	0	1	0	1	1	0	0	0	0	1	1	0	1	1	0	9	53%
De Vries & Drent (2004)	1	1	0	1	0	0	0	0	0	1	1	1	1	1	0	8	53%
Klonoff & Kleinhenz (1993)	1	1	0	0	0	0	1	0	0	1	1	1	0	1	0	7	47%
Wirnsberger et al. (1998b)	1	1	0	1	0	0	0	0	0	1	0	1	0	0	0	5	33%

Table 3 *Overview of studies on depression among sarcoidosis patients*

Study	Study quality	Major outcomes	Sample size (% male)	Age	Prevalence of depression % or *x*±SD	Assessment of depression	Conclusions about depression
Cox et al. (2004)	12	Depression	*n* = 120 (22%)	45	66%	CES-D	Outpatients with sarcoidosis showed a high prevalence of depression: 66%.
Drent et al. (1998)	12	Significant depression	*n* = 64 (58%)	43	18%	BDI	In sarcoidosis, QOL factors were associated with depressive symptoms.
Chang et al. (2001)	11	Clinical depression	*n* = 154 (21%)	47	60%	CES-D	Gender, income, access to medical care, dyspnea on exertion, and number of systems involved were associated with depression.
Wirnsberger et al. (1998a)	11	Significant depression	*n* = 64 (58%)	43	18%	BDI	In sarcoidosis, depressive symptoms were associated with psychological function (WHOQOL-100).
Antoniou et al. (2006)	11	Depression	*n* = 75 (31%, gender unknown: 33%)	50 ± 14	4.9 ± 5	HADS	There was no correlation between duration of disease and quality of wellbeing and anxiety and depression scales.
Goracci et al. (2008)	9	Major Depressive Disorder	*n* = 80 (45%)	46	25%	MINI-PLUS, DSM-IV axis I diagnosis	Twenty-five percent of the subjects met the criteria for Major Depressive Disorder.
Spruit et al. (2005)	9	Clinical depression	*n* = 22 (64%)	42	38%	HADS	Patients with sarcoidosis had higher anxiety and depression scores. Skeletal muscle weakness was related to, among other things, depression.
Yeager et al. (2005)	9	Depression	*n* = 736 (gender unknown)	-	46%	CES-D	Forty-six percent of sarcoidosis patients and 27% of controls had CES-D scores of ≥9. This was associated with decreased FVC and greater dyspnea.
De Vries & Drent (2004)	8	Depression	*n* = 1046 (37%, gender unknown: 4%)	45-49	10.2 ± 6.4	BDI	Depressive symptoms appeared to be related to perceived stress.
Klonoff & Kleinhenz (1993)	7	Depression	*n* = 17 (18%)	40	11.82 ± 8.52	BDI	Sarcoidosis patients as a group did not meet the generally accepted criterion for clinical depression.
Wirnsberger et al. (1998b)	5	Depressive symptoms	*n* = 1026 (37%)	47	17%	Questionnaire not standardized.	Sixteen percent of sarocoidosis patients reported familial sarcoidosis. Intervention programs should focus on psychosocial aspects.