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# Stiff Person Syndrome and Psychiatric Comorbidities: A Systematic Review

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**Abstract**

**Background**: Stiff person syndrome (SPS) is a rare autoimmune disease characterized by intermittent episodes of stiffness axial skeleton muscles. Patients with SPS may present with psychiatric symptoms and little is known about the presence of psychiatric comorbidities.
**Objective**: To provide an overview of the association between SPS and psychiatric illnesses.
**Methods**: The protocol is registered in PROSPERO (Registration ID CRD42020159354). Peer-reviewed articles published before May 26, 2020 on adults with SPS and psychiatric comorbidities were selected by two independent reviewers. Qualitative summary data and relative risk (RR) of psychiatric disorders in patients with SPS compared to the general population and multiple sclerosis (MS), another chronic autoimmune disorder, were calculated.
**Results**: After screening 909 articles, 52 full texts were assessed for eligibility and 27 were ultimately included, five of which were selected for quantitative analysis. The RR of any psychiatric comorbidity in SPS was higher than the general population ranging from 6.09 (95%CI: 4.09, 9.08) to 11.25 (95%CI: 3.27, 38.66). There was no statistically significant difference in the risk of any psychiatric comorbidity between SPS and MS, which is known to have a high prevalence of psychiatric illness. The review also highlighted delays in SPS diagnosis, often related to misattribution of symptoms as being solely secondary to a psychiatric cause.
**Conclusions**: The higher risk of psychiatric comorbidities emphasizes the important role of psychiatrists in recognizing the symptoms of SPS to reach timely diagnosis and treatment. The presence of psychiatric symptoms should support rather than delay the diagnosis of SPS.

**Key Words:** systematic review, stiff person syndrome, depression, anxiety, alcohol addiction, neurology, neuropsychiatry, consultation liaison psychiatry

## Introduction

Stiff Person Syndrome (SPS) and stiff limb syndrome (SLS) are exceedingly rare neurologic disorders with an estimated prevalence of one to two per million[1]. Patients experience fluctuating, painful rigidity, and spasms in the axial muscles which can be precipitated by unexpected noises, emotional stress, or tactile stimuli[1, 2]. The syndrome is associated with high levels of serum and cerebrospinal fluid autoantibodies against glutamic acid decarboxylase ($GAD_{65}$) which is the rate limiting enzyme for the synthesis of gamma-amino-butyric acid (GABA)[3], a major neurotransmitter associated with inhibitory synaptic signaling. The proposed pathogenesis of SPS involves antibodies against $GAD_{65}$ causing low levels of GABA and consequent disinhibition, leading to the symptomatology of SPS[4].

Patients with SPS often present to psychiatrists with nonspecific symptoms of depression and anxiety, and therefore it is important for psychiatrists to be familiar with the diagnosis of SPS[5]. Additionally, neurologic symptoms of SPS can be misdiagnosed as a psychogenic movement disorder, leading to delays in adequate treatment[6-8]. Several case reports have described patients with SPS having severe comorbid psychiatric symptoms, leading to challenges in diagnosis and treatment[9, 10]. To our knowledge, there is no systematic review summarizing published evidence of SPS and its association with psychiatric illnesses.

The goal of this systematic review is to gather data from publications in which patients are diagnosed with SPS/SLS and psychiatric illnesses. This data gathered is contrasted with known prevalence of psychiatric disorders to better understand a possible association with SPS.

## Methods

*Protocol and registration, search, information sources*

This systematic literature review follows the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines[11], and the PRISMA Elaboration and Explanation[12]. (**See eSupplement 1: PRISMA Checklist**). The planned methodology is registered in PROSPERO (Registration ID CRD42020159354)[13]. Details of the protocol and registration are published as online supplemental material. (**See eSupplement 2: Protocol and Registration**). The search period covered the years from inception to May 26, 2020 through the following online databases: PubMed, Embase Ovid Platform, and Cochrane Central. (**See eSupplement 3: Search Strings**). The results were compiled and duplicates removed using EndNote X9.

*Eligibility criteria*

Due to the scarcity of data on SPS, no restrictions were placed on study design or publication date, however titles that were published as posters or abstracts alone without a peer-reviewed manuscript were excluded. English and French languages were included. Studies were selected for inclusion if they: (1) were an original article in a peer-reviewed journal; (2) described human subjects; (3) who were 18 years or older; (4) had a diagnosis of SPS or SLS, and (5) had a diagnosis of one or more psychiatric illnesses.

*Study selection*

Two blinded reviewers (C.A. and D.C.) screened abstracts against eligibility criteria, with discordance resolved by a blinded third reviewer (C.F.) who acted as a tiebreaker. Full texts of selected abstracts were then reviewed by the two independent reviewers, with discordance resolved using the tie breaker. The reference lists of all articles selected for inclusion were examined, and additional full texts were included as appropriate.

*Data collection process, Data items*

Data was extracted by one reviewer (D.C.) and assessed by a second reviewer (C.A.) in a structured form, and discordance was resolved by discussion. Data extracted included patient age, gender, timeline of SPS and psychiatric diagnoses, and method of these diagnoses. Psychiatric diagnoses were grouped by DSM-V category to calculate main effect measures, including depressive disorders (major depressive disorder and dysthymia), anxiety disorders (generalized anxiety disorder, specific phobia, agoraphobia), and alcohol related disorders (alcohol use disorder and alcohol dependence of history of dependence). When possible, data was extracted at the level of individual patients, and when individual patient data was not provided, authors were contacted for individual patient data. Grouped data was included when individual data could not be retrieved.

*Risk of bias*

The quality of evidence of each included study was assessed by C.A. and D.C. independently, with discordance resolved by discussion. The Oxford Centre for Evidence-Based Medicine levels of evidence guide was utilized to compare study designs categorically[14], and the Joanna Briggs Institute (JBI) critical appraisal checklists used to compare the quality of information and risk of bias within study designs[15]. Due to the low prevalence of SPS, we expected few high-quality study designs on this topic. We anticipated many aspects of bias common to retrospective, observational studies, including no possibility to establish cause-effect relationship, danger of over-interpretation, and recall bias. Publication bias was also a significant limitation, over-representing data more toward the unusual rather than common clinical presentations of SPS.

*Summary measures, Synthesis of results, Additional analysis*

The primary study measure was the relative risk (RR) of psychiatric disorders. RR was calculated when studies had the following methodological criteria: Studies included multiple patients recruited based on exposure (SPS diagnosis) and evaluated for the following effect measures: psychiatric diagnoses of depressive, anxiety and/or alcohol use disorders. Relative risks were then calculated utilizing two comparator groups and their respective prevalence of psychiatric illness. General population data from the National Survey on Drug Use and Health (NSDUH)[16] and the National Institute of Mental Health (NIMH)[17] was used as the first comparator group for prevalence of depressive/alcohol use disorders and anxiety disorders respectively. A systematic review by Marrie et al. which estimated the prevalence of psychiatric disorders in patients with multiple sclerosis (MS) was utilized as the second comparator group[18]. This second comparator group was selected as, similar to SPS, MS is a chronic and debilitating disorder with an autoimmune etiology. Comparisons were made using Fisher's exact tests, and

the confidence intervals were calculated based on Koopman's asymptomatic scores. Q and $I^2$ statistics for heterogeneity assessment could not be completed due to wide structural variations in study designs.

## Results

*Study selection*

A total of 23 articles met eligibility criteria out of 909 unique publications. Of the 23 selected for inclusion, references were scanned, and 4 were additionally selected for inclusion, leading to 27 articles in total included. (**See Figure 1: Flow Diagram**).

*Study characteristics & Results*

The 27 studies considered include: seventeen case reports of individual patients[6-10, 19-30], four case series (including 2, 2, 4, and 12 patients)[31-34], five cross sectional studies (including 8, 9, 13, 24 patients)[35-39] and one prospective cohort study (including 99 patients)[40]. (**See Table 1: Characteristics and Results of Studies**). Five studies had appropriate methodology to calculate relative risks (RR) of psychiatric disorders compared to the general population and MS[35-38, 40]. (**See Figure 2: Forest Plots showing Relative Risk (RR) and 95% Confidence Interval (95% CI) of Psychiatric Comorbidities in SPS**).

RR of any psychiatric disorder in SPS (which included any DSM-V or equivalent diagnosis) compared to the general population was statistically significant in all five studies, ranging from estimates of 6.09 (95%CI: 4.09, 9.08)[40] to 11.25 (95%CI: 3.27, 38.66)[35]. However, when compared to MS, the rate of any psychiatric illnesses in SPS showed no statistical significance, with RR ranging from 0.80 (95%CI: 0.53, 1.19)[40] to 1.47 (95%CI: 0.43, 5.04)[35].

RR of depression compared to the general population was statistically significant in all but one study[38], with estimated RRs ranging from 3.06 (95%CI: 1.87, 5.02)[40] to 18.03 (95%CI: 8.18, 39.75)[37]. When compared to MS, the probability of a diagnosis of depressive disorders was only significantly higher for SPS patients in one of five studies, with RR of 4.51 (95%CI: 2.04, 9.94)[37].

RR of anxiety disorders were similar when compared to both the general population and MS, with only one study showing significantly elevated RR in SPS, with RR of 3.33 (95%CI: 1.84, 6.01) compared to the general population and of 2.82 (95%CI: 1.56, 5.11) compared to MS[38].

Alcohol use disorders were similar to the general population in two of three studies[35, 40], and elevated in one study with RR of 7.79 (95%CI: 2.54, 23.82)[36], whereas when compared to MS, the probability of a diagnosis of an alcohol use disorder was decreased in SPS in one study with RR of 0.37 (95%CI: 0.17, 0.83)[40], and similar in the other two[35, 36].

Of the seventeen case reports, fifteen described females[6-10, 19-30] and two described males[29, 30]. The age range was 22 to 58 years, (mean age: 42 years (SD +/- 11 years)). Major depressive disorder was described in eight cases[10, 20-24, 26, 27], generalized anxiety disorder in nine[7, 9, 10, 19-22, 27, 28], panic attacks in six[6, 8, 10, 25, 27], phobia in six[6, 19, 20, 25, 28, 30], post traumatic stress disorder in two[23, 25], a single case of each: bipolar disorder[25], social anxiety disorder[29], and anorexia

nervosa[22]. Ten of the seventeen case reports specifically discussed difficulty or delay in reaching SPS diagnosis due to the presence of psychiatric symptoms[6-8, 20-23, 26, 27, 30], with five patients having their symptoms initially explained as secondary to psychiatric causes[8, 22, 26, 27, 30]. (**See eTable 1: Psychiatric Diagnoses Confounding or Delaying Stiff Person Syndrome Diagnoses).**

The four case series studies included twenty patients, fifteen of whom were female and five were male. The age range was 30 to 65 years (mean age: 45 years (SD+/-10 years))[31-34]. Benavides et al. described two patients with SPS diagnosed with anxiety disorder and depression, respectively[31]. Marano et al. discussed two patients diagnosed with SPS, one with anxiety and depression, and the other with generalized anxiety disorder and pseudoagoraphobia[32]. Both patients experienced delays in diagnosis of SPS, with the first delay being five years after SPS symptom onset and was initially diagnosed with psychogenic movement disorder. The second endured a delay of four years and was initially diagnosed with a psychogenic gait disorder. McEvoy et al. described two patients diagnosed with SPS, one with co-morbid recurrent depressive episodes and one with a delay in his diagnosis of SPS by several years due to symptoms being attributed to alcohol and benzodiazepine dependence[33]. Tinsley et al. described twelve cases of SPS[34] including four cases of major depression, one of generalized anxiety disorder, two of phobias, four of current or history of alcohol abuse, and three of personality disorders. Three of these patients were initially diagnosed with psychiatric disorders alone before being found to have SPS. The three cases with the longest delays in diagnosis included delays of 8, 15 and 20 years after symptom onset, with delays related to initial misdiagnosis of conversion disorder, and previous psychiatric hospitalizations[34]. Additionally, one cross sectional study Henningsen et al.[39] included 8 patients, (6 F, 2 M), ages 33-68, mean age 54, and included three cases of agoraphobia, one with agoraphobia and subacute depression, and two with claustrophobia and agoraphobia.

*Risk of bias*

Risk of bias assessments for each individual study can be found in **Table 2: Summary of Critical Appraisals**. Additionally, the detailed checklists of criteria fulfilled for each study is published as online supplemental material. (**See eSupplement 4: Checklists for Critical Appraisals)**. In summary, the seventeen case reports[6-10, 19-30] were rated as level 5 evidence (lowest quality design, highest risk of bias) by the Oxford Quality Rating Scheme[14]. When assessed in more detail by the Joanna Briggs Institute (JBI) Critical Appraisal for Case Reports[15], most were assessed as high quality, with eleven meeting 8 of 8 criteria[6, 8, 9, 19-21, 23, 24, 26-28], five meeting 7 of 8 criteria[7, 10, 22, 25, 30] and one meeting 6 of 8 criteria[29]. The four case series studies[31-34] were rated as level 4 evidence by the Oxford Quality Rating Scheme[14]. They were then further described using the JBI Critical Appraisal for Case Series Studies[15], with one meeting 9 of 10 criteria[34], one meeting 7 of 10 criteria[32], one meeting 6 of 10 criteria[31], and one meeting only 5 of 10 criteria[33]. The five cross sectional studies[35-39] were rated as level 4 evidence by the Oxford Quality Rating Scheme[14]. Using the JBI Critical Appraisal for Cross Sectional Studies[15], one met 8 of 8 criteria[38], two met 7 of 8 criteria[36, 37], one met 6 of 8 criteria[35], and one met 5 of 8 criteria[39]. Finally, one cohort study[40] was rated as level 2 evidence by the Oxford Quality Rating Scheme[14], and met 9 of 11 criteria of the JBI Critical Appraisal for Cohort

Studies[15]. When assessing bias across the included studies, we noted that the majority of these studies were retrospective, observational studies, with biases including recall bias. Publication bias was also a significant limitation, over-representing data more toward the unusual rather than common clinical presentations of SPS. The interpretation of these results is therefore limited by these factors.

## Discussion

This review estimates a significantly higher risk of psychiatric illnesses in patients with SPS compared to the general population. The risk was similar to that of MS, which is known to have a high prevalence of psychiatric co-morbidities[18]. As patients with SPS often initially present to primary care physicians or psychiatrists, it is important for all clinicians – and not just neurologists – to be aware of this diagnosis.

While we did not find consistently, significantly elevated risks of anxiety disorders in the four studies meeting methodology criteria for RR calculations[35-38, 40], there were many case reports and case series that outlined generalized anxiety[7, 9, 10, 19-22, 27, 28, 31, 32, 34], phobia[6, 19, 20, 25, 28, 30, 32, 34], and panic attacks[6, 8, 10, 25, 27] as symptoms and comorbidities. Phobia, in particular, has been documented as a common diagnostic clue to support SPS, especially to situations that could lead to falls (open spaces, crossing the street, etc)[38]. Additionally, Cervantes et al. noted that the DSM-V criteria for generalized anxiety disorder and for SPS have several similar and overlapping symptoms, including stiffness, fatigue, muscle tension, and overlapping responses to treatment with benzodiazepine[7]. Noting that anxiety disorders are commonly comorbid in patients with SPS is therefore important for both diagnostic and therapeutic purposes.

This review also suggests that patients with SPS appear to be at high risk of depressive disorders compared to the general population, based on both our primary effect measure of significantly elevated RR compared to the general population as well as on subjective data from case reports and case series[10, 20-24, 26, 27, 31-34]. Compared to anxiety and phobias, less has been written about SPS and depression. Gerschlager et al. assessed for quality of life metrics including the Beck Depression Inventory in 24 patients with SPS, and found ten of these patients to have mild to moderate depression, and four to have moderate to severe depression [37].

Based on this review, many studies describe significant delays in SPS diagnosis in part due to initial misdiagnoses or misattribution of SPS symptoms[6-8, 20-23, 26, 27, 30, 32-34, 36, 38-40]. These reports often follow a similar patient trajectory in which the patients' symptoms are initially diagnosed as conversion disorder, psychogenic movement disorder, panic disorder, or another anxiety disorder. During that time, patients may receive inadequate treatment for SPS, which could, in turn, worsen quality of life and contribute to anxiety, depression, and substance use disorders.

The rarity of SPS compounds the diagnostic challenge it imposes, further raising concerns that its overall prevalence could be underestimated[1]. In an effort to follow best diagnostic principles, and find a parsimonious pathology to explain the list of a patient's symptoms, clinicians may anchor to psychiatric symptoms when encountering a patient presenting with SPS. Rather than

confounding the diagnosis, we are proposing the possibility that the presence of psychiatric symptoms supports the diagnosis of SPS rather than detract from it.

Certainly, a challenging illness such as SPS can worsen quality of life leading to a higher risk of psychiatric comorbidities. Furthermore, the pathophysiology of SPS overlaps with that of several psychiatric illnesses. A number of publications attribute the psychiatric relevance of SPS to reduced or impaired GABAergic inhibition. In fact, impaired GABAergic transmission is suggested to underlie many psychiatric disorders, including anxiety disorders, sleep disorders, depression, substance use disorders, and posttraumatic stress disorder[7, 9, 21-23, 26, 27, 34, 36].

Our review was limited by the lack of large controlled studies, in part due to the rarity of SPS as a diagnosis. Small sample sizes lead to low powered analysis and wide confidence intervals of our RR estimates. Additionally, utilizing an external comparator group rather than a control group within each study leads to shortcomings including changes in DSM criteria over the publication years, variation in study sample, design, and settings. Cohort studies involving larger groups of SPS patients are needed in order to better understand and quantify psychiatric comorbidities.

## Conclusion

This systematic review found that patients with SPS are at a significantly higher risk of psychiatric comorbidities than the general population. Additionally, there can be a significant delay in SPS diagnosis, sometimes due to misattribution of symptoms. It is important for clinicians to be aware of that overlap, and rather than confounding the diagnosis, the presence of psychiatric symptoms supports the diagnosis of SPS.

## Conflict of Interest Statement

The authors have no conflicts of interest to disclose. No grants or any other financial support were provided for this manuscript.

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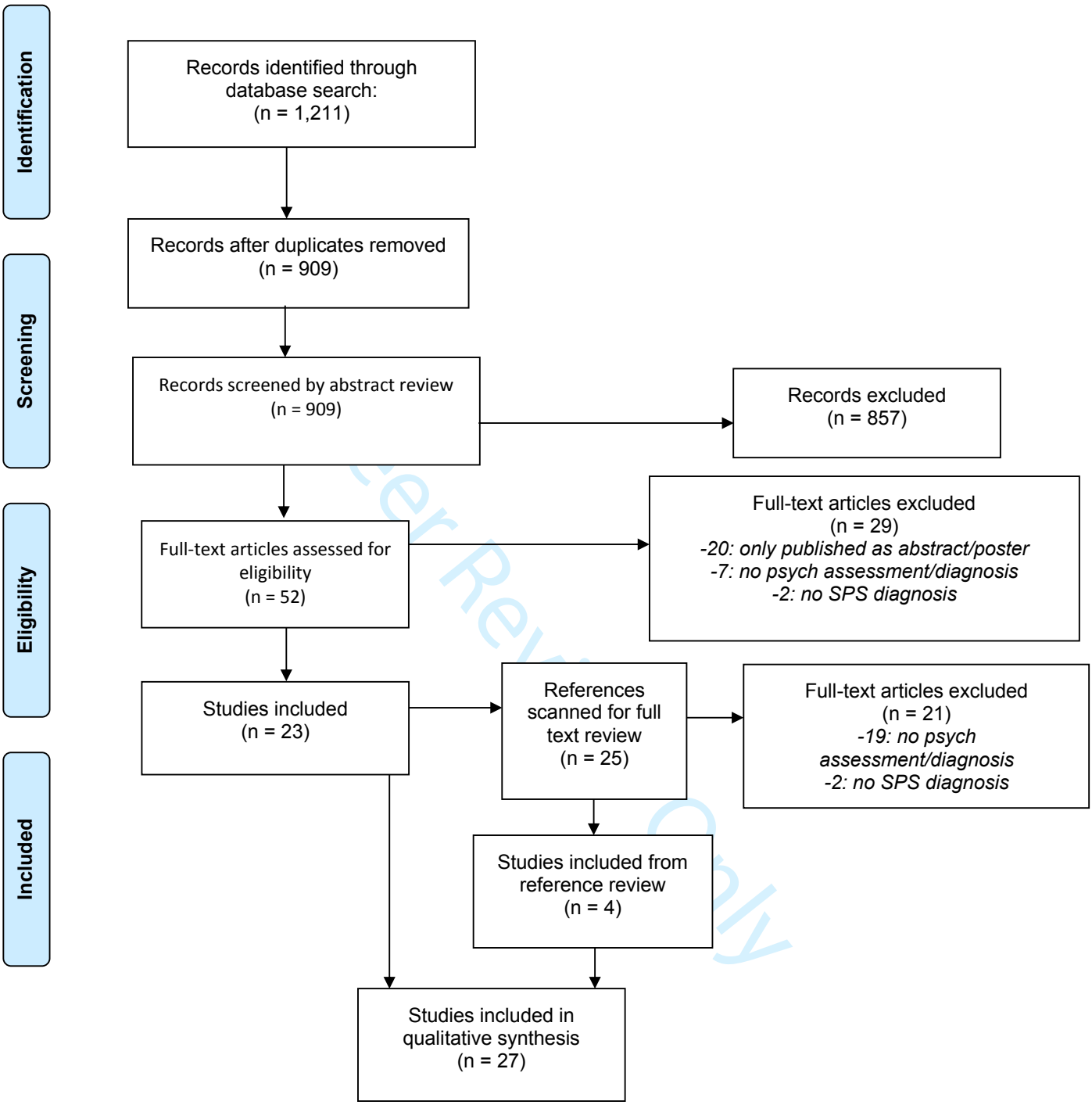
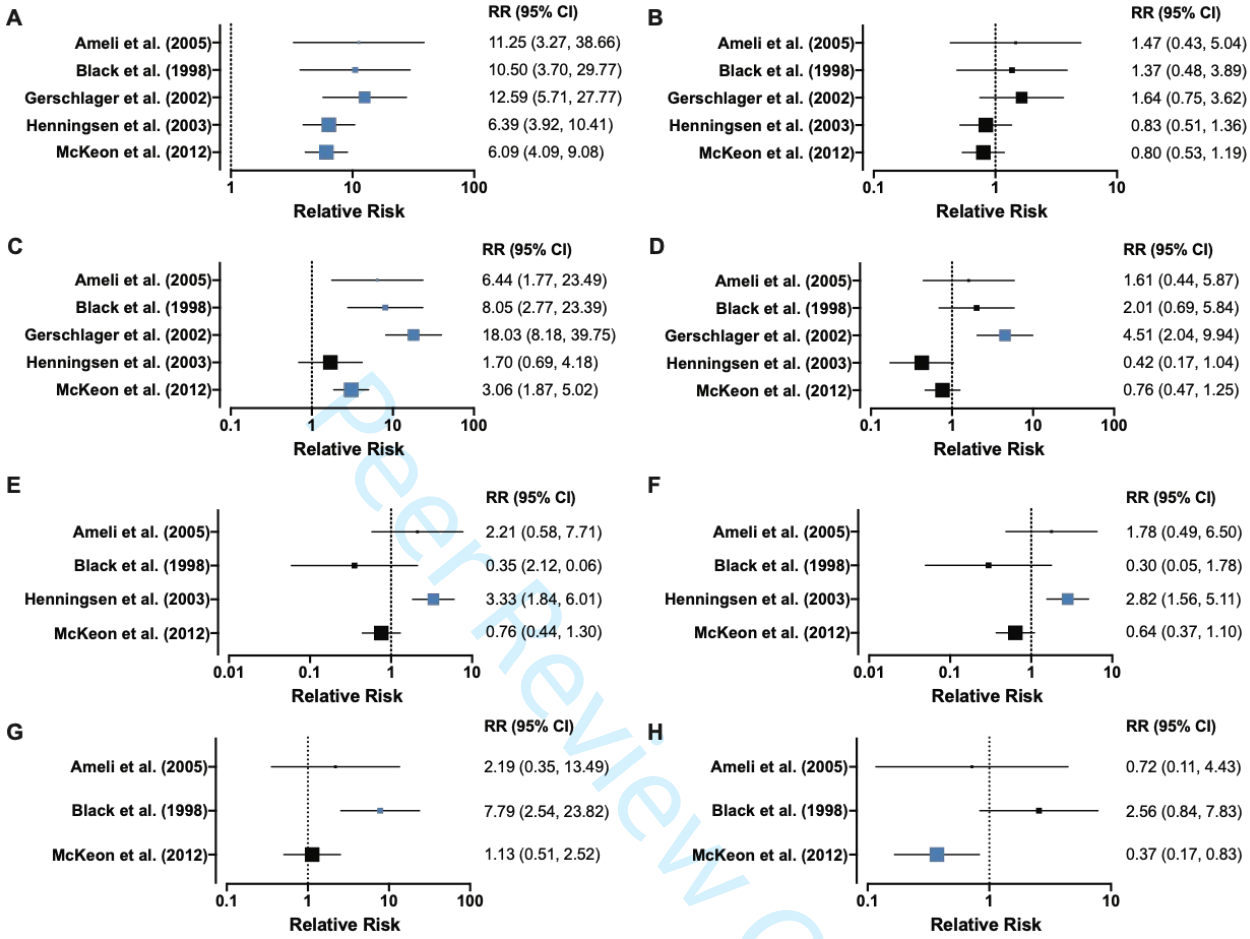
**Figure 1: Flow Diagram**




From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta *A*nalyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

**Figure 2: Forest Plots showing Relative Risk (RR) and 95% Confidence Interval (95% CI) of Psychiatric Comorbidities in Stiff Person Syndrome (SPS)**




Forest Plot A: Relative risk (RR) of any psychiatric disorder in patients with SPS to the general population.
Forest Plot B: RR of any psychiatric disorder in patients with SPS compared to patients with multiple sclerosis (MS).
Forest Plot C: RR of depressive disorders in patients with SPS compared to the general population.
Forest Plot D: RR of depressive disorders in patients with SPS compared to patients with MS.
Forest Plot E: RR of anxiety disorders in patients with SPS compared to the general population.
Forest Plot F: RR of anxiety disorders in patients with SPS compared to patients with MS.
Forest Plot G: RR of alcohol use disorders in patients with SPS compared to the general population.
Forest Plot H: RR of alcohol use disorders in patients with SPS compared to patients with MS.

The x-axis is the log 10 of the Relative Risk
The size of the squares are proportional to the power of the study, and the blue color indicates statistical significance.
Comparisons were made using Fisher's exact tests, and the confidence intervals were calculated based on Koopman's asymptomatic score.

***[Note to editor: Print image in color]***

**Table 1: Characteristics and Results of Studies**

| Reference | Study Design | Number of Patients | Gender/Age of Patients | Psychiatric Diagnosis | Method of Diagnosis |
|---|---|---|---|---|---|
| Andreadou et al. | Case Report | 1 | 41 year-old F | panic disorder, agoraphobia | DSM-IV |
| Cerqueira et al. | Case Report | 1 | 51-year old F | generalized anxiety disorder | DSM-IV |
| Cervantes et al. | Case Report | 1 | 30-year-old F | generalized anxiety disorder, recurrent panic attacks | Not described |
| Chang et al. | Case Report | 1 | 55-year-old F | general anxiety disorder, specific phobia, agoraphobia | Not described |
| Cobb et al. | Case Report | 1 | 22-year-old F | general anxiety disorder, major depressive disorder, insomnia, specific phobia | Not described |
| Culav-Sumic et al. | Case Report | 1 | 55-year-old F | major depressive disorder, possibly generalized anxiety disorder | Not described |
| Cuturic et al. | Case Report | 1 | 35-year-old F | anorexia nervosa, major depression, and anxiety disorder | Not described |
| Dinnerstein et al. | Case Report | 1 | 50-year-old F | major depression, post traumatic stress disorder | DSM-IV |
| Ho et al. | Case Report | 1 | 43-year-old F | Prolonged grief, panic attacks | DSM-IV |
| Kiriakos et al. | Case Report | 1 | 36-year-old F | major depression, generalized anxiety, and panic disorder | DSM IV |
| Morris et al. | Case Report | 1 | M, age unknown | social anxiety | Interview, Questionnaire |
| Munhoz et al. | Case Report | 1 | 48-year-old F | major depression | Not described |
| Patel et al. | Case Report | 1 | 58-year-old F | panic disorder, agoraphobia, bipolar I disorder, posttraumatic stress disorder | Not described |
| Pretorius et al. | Case Report | 1 | 45-year-old F | major depression | Not described |
| Sablaban et al. | Case Report | 1 | 32-year-old F | panic disorder, major depression, generalized anxiety disorder | DSM V |
| Souissi et al. | Case Report | 1 | 36-year-old M | unspecified "psychiatric disorder," symptoms of phobia | Not described |
| Wilson et al. | Case Report | 1 | 28-year-old F | generalized anxiety with agoraphobia | Not described |

| Reference | Study Design | Number of Patients | Gender/Age of Patients | Psychiatric Diagnoses | Method of Diagnosis |
|---|---|---|---|---|---|
| Benavides et al. | Case Series | 4 | 51-year-old F<br>38-year-old F<br>49-year-old F<br>30-year-old M | 1 with anxiety disorder<br>1 with depression<br>2 without psychiatric diagnoses | Not described |
| Marano et al. | Case Series | 2 | 60-year-old F<br>65-year-old F | 1 with anxiety and depression<br>1 with generalized anxiety disorder and pseudoagoraphobia | Hamilton depression and anxiety Scales |
| McEvoy et al. | Case Series | 2 | 33-year-old F<br>40-year-old M | 1 with recurrent depressive episodes<br>1 with alcohol and benzodiazepine dependence | Not described |
| Tinsley et al. | Case Series | 12 | (9 F, 3 M), mean age 45, SD 7.7 years | 1 with anxiety disorder<br>1 with adjustment disorder<br>2 with major depression<br>1 with depression, phobic anxiety<br>1 with alcohol dependence, simple phobia<br>1 with history of alcohol abuse<br>1 with depression, dependent personality disorder, and alcohol dependence<br>1 with dependent personality disorder, history of alcohol dependence<br>1 with personality disorder<br>2 with no psychiatric diagnosis | DSM-IV |
| Henningsen et al. (1996) | Cross Sectional | 8 | (6 F, 2 M), ages 33-68, mean age 54 | 3 with agoraphobia<br>1 with agoraphobia and subacute depression<br>2 with mild claustrophobia and agoraphobia<br>2 with no psych diagnosis | Not described |
| Henningsen et al. (2003) | Cross Sectional | 43 | Of 43 patients, 25 SPS/SLS, 13 PERM, and 3 pSPS<br><br>(29 F, 14 M), ages 18-75, mean age 53, SD = ± 13.8 | 19 patients had task specific phobia<br>6 had anxiety and/or adjustment disorders (2 with generalised anxiety disorder)<br>5 with major depression or dysthymia<br>6 with personality disorders<br>4 with other psychiatric disorders (substance abuse, mild dementia).<br>specifically: 11 SMS with phobia, 10 without. 1 SLS with phobia, 2 without. | DSM IV |

| Reference | Study Design | Number of Patients | Gender/Age of Patients | Psychiatric Diagnoses | Method of Diagnosis |
|---|---|---|---|---|---|
| Gerschlager et al. | Cross Sectional | 24 | (14 F, 10 M) mean age 53, SD ± 9.5 | 10 patients had mild to moderate depression, 4 patients had moderate to severe depression 10 patients had no depression | Beck depression Inventory (BDI) |
| Ameli et al. | Cross Sectional | 9 | (7 F, 3 M), ages 35-60, mean age 52 | 2 with depression<br>1 with alcohol dependence<br>1 with social phobia<br>1 with dysthymia, post traumatic stress disorder, cannabis use disorder, crystal meth dependence<br>4 with no psych diagnosis | DSM-IV |
| Black et al. | Cross Sectional | 13 | (8 F, 5 M), ages 35-68, mean age 47 | 2 with depression<br>1 with depression, alcohol abuse<br>1 with depression, alcoholism, anxiety<br>1 with depression, conversion disorder, alcohol abuse<br>1 with alcohol abuse<br>1 with adjustment disorder<br>1 with conversion disorder<br>5 with no psych diagnosis | DSM-III |
| McKeon et al. | Prospective Cohort | 99 | Of 99 patients, 96 SPS/SLS, 3 PERM.<br><br>(67 F, 32 M), ages 5-70, median age 40 | 12 with anxiety disorder<br>19 with depression<br>6 with alcohol dependence<br>3 with social phobia or agoraphobia | Not described |

## Table 2: Summary of Critical Appraisals

| Reference | Oxford Quality Rating Scheme[14] | JBI criteria fulfilled[15] |
|---|---|---|
| Andreadou et al. | 5 | 8 of 8 |
| Cerqueira et al. | 5 | 8 of 8 |
| Cervantes et al. | 5 | 7 of 8 |
| Chang et al. | 5 | 8 of 8 |
| Cobb et al. | 5 | 8 of 8 |
| Culav-Sumic et al. | 5 | 8 of 8 |
| Cuturic et al. | 5 | 7 of 8 |
| Dinnerstein et al. | 5 | 8 of 8 |
| Ho et al. | 5 | 8 of 8 |
| Kiriakos et al. | 5 | 7 of 8 |
| Morris et al. | 5 | 6 of 8 |
| Munhoz et al. | 5 | 8 of 8 |
| Patel et al. | 5 | 7 of 8 |
| Pretorius et al. | 5 | 8 of 8 |
| Sablaban et al. | 5 | 8 of 8 |
| Souissi et al. | 5 | 7 of 8 |
| Wilson et al. | 5 | 8 of 8 |
| Ameli et al. | 4 | 6 of 8 |
| Benavides et al. | 4 | 6 of 10 |
| Black et al. | 4 | 7 of 8 |
| Marano et al. | 4 | 7 of 10 |
| McEvoy et al | 4 | 5 of 10 |
| Gerschlager et al | 4 | 7 of 8 |
| Henningsen et al. (2003) | 4 | 8 of 8 |
| Henningsen et al. (1996) | 4 | 5 of 8 |
| Tinsley et al. | 4 | 9 of 10 |
| McKeon et al. | 2 | 9 of 11 |

Two appraisal tools were utilized to assess for bias: Column 1 utilized the Oxford Quality Rating Scheme[14], with high quality study designs designated as lower numbers respectively: cohort studies (Oxford score = 2, 3); cross sectional studies (Oxford score = 4); case series (Oxford score = 4); case reports (Oxford score = 5). Column 2 summarizes the number of criteria fulfilled in the Joanna Briggs Institute (JBI) critical appraisal tools[15], (Cohort studies JBI criteria out of 11, cross sectional studies out of 8, case series studies out of 10, and case report studies out of 8), with a higher number of criteria fulfilled representing more thorough information and higher quality design.