



## **The psychological impact of Stevens- Johnson syndrome and toxic epidermal necrolysis on patients' lives: a critically appraised topic**

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## **The psychological impact of Stevens-Johnson syndrome and toxic epidermal necrolysis on patients' lives: A critically appraised topic**

### **Short Title:**

The psychological impact of SJS and TEN on patients: A critically appraised topic

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### **Conflicts of interest**

None declared

### **Bulleted statements (max 70 words per question)**

- a. What's already known about this topic?
  - Many long-term sequelae have been identified with cutaneous and ocular problems being amongst the most common
  - A search of existing literature has identified a lack of research relating to the psychological impact on patients
- b. What does this study add?
  - SJS and TEN have long lasting psychosocial implications for the lives of those affected and their significant others
  - Health care practitioners' (HCP) lack of information around the disorder particularly in terms of its diagnosis caused stress and anxiety for patients

- Following discharge from the hospital, individuals expressed fear of taking medication and in attending their doctor, frequently leading them to engage in avoidance behaviours
- Patients were distressed with symptoms aligned to PTSD

## Abstract

**Clinical scenario** A 65 year-old male presented with a 12 hour history of deteriorating rash. Two weeks previously, he had completed a course of neo-adjuvant chemotherapy for ductal carcinoma of the breast. On examination, there were bullae, widespread atypical targetoid lesions and 15% epidermal detachment. There was no mucosal involvement on presentation but, subsequently, it did evolve. Skin biopsy showed sub-epidermal blistering with epidermal necrosis. This confirmed our clinical diagnosis of overlap SJS-TEN. On transfer to ICU, he was anxious and fearful.

What are the psychological impacts of SJS/TEN on this man's life?

**Background** SJS and TEN have devastating outcomes for those affected.



**Objectives** To conduct a critically appraised topic (CAT) to (1) analyse existing research related to the psychological impact of SJS and TEN and (2) apply the results to the clinical scenario.

**Methods** Seven electronic databases were searched for publications focusing on the psychological impact of SJS TEN on adults over 18 years of age.

**Results** Six studies met inclusion criteria. Health care practitioners' (HCPs) lack of information around the disorder was highlighted. Patients experienced undue stress and fear. Some patients had symptoms aligned to post-traumatic stress disorder (PTSD), anxiety and depression.

**Discussion and recommendation for clinical case** The evidence suggests that SJS and TEN impact psychologically on patients' lives. Education of HCPs, to address their lack of awareness and information on SJS/TEN, should facilitate their capacity to provide information and support to patients, thereby reducing patient anxiety. On discharge, a follow up appointment with relevant HCPs to reduce the possibility of PTSD occurring should be considered.

### **Clinical scenario**

A 65 year-old male presented as being acutely unwell with a 12 hour history of deteriorating rash. In the preceding two weeks, he had completed a course of neo-adjuvant chemotherapy for locally advanced invasive HER2 positive ductal carcinoma of the left breast. His medications included his chemotherapy agents viz. docetaxel, carboplatin and trastuzumab as well as intermittent dexametasone and domperidone. On examination, there were bullae, widespread atypical targetoid lesions and 15% epidermal detachment. There was no mucosal involvement on presentation but, subsequently, it did

evolve. Skin biopsy showed sub-epidermal blistering with epidermal necrosis. This confirmed our clinical diagnosis of overlap SJS-TEN. His SCORTEN (SCORE of Toxic Epidermal Necrosis) was four; with a projected mortality risk of 58%. On transfer to ICU, he was anxious and fearful.

What are the psychological impacts of SJS/TEN on this man's life?

## Background

SJS and TEN are severe immune mediated mucocutaneous reactions, usually occurring as a result of medications.<sup>1</sup> Many medications have been identified as causing the conditions some of which include allopurinol,<sup>2-4</sup> sulphonamide antibiotics,<sup>3</sup> anticonvulsant agents,<sup>4</sup> oxicam, nonsteroidal anti-inflammatory drugs,<sup>3</sup> chlormezanone,<sup>4</sup> corticosteroids<sup>4</sup> and nevirapine.<sup>3</sup> Some 'over-the-counter' medications, such as acetaminophen, metamizole and ibuprofen, have also been linked to the conditions.<sup>2, 5, 6</sup> However, Roujeau *et al.*<sup>7</sup> highlight that the link between medications, such as acetaminophen, ibuprofen and secretolytics in causing SJS and TEN, may be as a result of protopathic bias. These conditions can be linked to infections such as HIV,<sup>8</sup> herpes virus<sup>9</sup> and mycoplasma pneumonia.<sup>10</sup> A rare genetic predisposition (the genotype HLA-B\*1502), which only occurs in persons of Chinese and Southeast-Asian descent, is linked to causing the conditions where the genotype reacts with an environmental trigger viz. the absorption of carbamazepine.<sup>11</sup> SJS and TEN are characterised, in the acute phase, by a febrile illness followed by cutaneous erythema with blister formation, skin and mucous membrane necrosis and detachment.<sup>12</sup> The individual becomes critically ill within a short period of time and is treated as a medical emergency. The United Kingdom guidelines and French national care protocols, for the management of SJS and TEN, have noted that, if patients are not referred to a specialist area such as an Intensive Care Unit (ICU) or Burns Centre, the mortality outcome for the patient may be affected.<sup>1, 13</sup> SJS and TEN are on the same disease continuum.<sup>14</sup> A severity of illness score viz. SCORTEN, which is calculated on days one and three, is a measure for determining the seriousness of the conditions.<sup>15</sup> In SJS, a body surface area (BSA) of < 10% is affected; in the case of TEN  $\geq 30\%$  of the body surface is affected, whilst in-between is referred to as SJS/TEN overlap.<sup>16</sup> Sekula *et al.*<sup>17</sup> reported mortality rates of 23% and 34% at six weeks and one year, respectively.

The literature indicates that these conditions are rare in the general population viz. 1-2 per million per year.<sup>18, 19</sup> A United Kingdom (UK) study of SJS/TEN has highlighted an incidence rate of 5.76 SJS/TEN

cases per million person-years between 1995 and 2013.<sup>20</sup> The study has noted that the incidence rate has been higher in patients aged under 10 years and 80 years or older. An increased susceptibility to SJS, in patients over 80 years, may be partly explained by polypharmacy within this age cohort.<sup>21</sup> Difficulties in differentiating between erythema multiforme majus and SJS in these age groups may account for the higher incidence rates.<sup>22, 23</sup>

Notwithstanding the rarity of the conditions outlined above, they have devastating outcomes for those affected. Many long-term sequelae have been identified, with cutaneous and ocular problems being amongst the most common;<sup>24</sup> respiratory and gastrointestinal tracts may also be affected.<sup>25</sup> At the onset, the focus of care is on preservation and maintenance of life. Whilst the British Association of Dermatologists (BAD) guidelines provide comprehensive details on the medical care and management of adult patients with SJS and TEN, authors have recommended further research into what constitutes optimal supportive care.<sup>1</sup> According to Nogueira *et al.*,<sup>26</sup> the conditions have significant psychological effects on the patients, causing them distress and anxiety. The French national diagnosis and care protocol for SJS and TEN refer to the importance of managing pain and psychological distress.<sup>13</sup> However, a search of existing literature has identified a dearth of research relating to the psychological impact of SJS and TEN on patients. According to Lee *et al.*,<sup>25</sup> the long-term psychiatric and psychosocial sequelae of SJS and TEN remain unclear.

The objective of this CAT is (1) to critically appraise existing research related to the psychological impact of SJS and TEN and (2) apply the results to the patient scenario.

## Methods

A CAT was completed based on the four main steps outlined by Callander *et al.*<sup>27</sup>

### 1. Formation of a focused question:

The original question arose from clinical practice. Using the Population, Exposure, Outcome/Theme (PEO) format we devised a review question.<sup>28, 29</sup> We considered empirical evidence, which focused on:

(P) Adults over 18 years of age presenting with SJS or TEN

(E) Adverse reaction diagnosed as SJS or TEN

(O) Psychological impact such as emotional upset/trauma, post-traumatic stress, anxiety, or other impact on individuals' well-being and self-concept (Table S1; see Supporting Information).

## 2. Search for the best available evidence:

Following the PRISMA guidelines,<sup>30</sup> a systematic search was conducted sourcing and synthesising empirical evidence which used qualitative and/or quantitative research.<sup>29</sup> The protocol for this review has been registered with the International Prospective Register of Systematic Reviews (PROSPERO) (CRD42018111369).<sup>31</sup>

The CAT used the integrative review methodological process outlined by Whittemore and Knafl.<sup>29</sup> This method facilitated the concurrent synthesis of qualitative and quantitative empirical evidence, which was necessary to answer our clinical question. Qualitative and quantitative empirical studies were included, and unpublished research theses and dissertations.

We searched seven electronic international databases for publications and identified additional records through other sources, dating from January 2008 to December 2018 (Fig. 1). The search strategy was developed through consensus across the review team. Two information specialists (Librarians) (ID & LD) were on the review team and led on the search process. We carried out a preliminary search on Medline to determine the sensitivity and accuracy of selected search terms. The search terms included synonyms and Medical Sub-Headings (MeSH) describing SJS and TEN and psychological impact. We exported all records to EndNote and removed duplicates and studies outside of the date range.

Fig 1.

Adhering to the inclusion and exclusion criteria, five authors (PO'R; CK; PM; ID; SR) screened the titles and abstracts (n=937) with four working in pairs and one reviewer (CK) acting as arbitrator, if required. Review meetings were held to discuss outcomes and to agree on final studies for the next stage of the

process viz. full text review (n=33). Two reviewers screened full text articles and a meeting was held to agree on the rationale for exclusion of studies. Six studies, which met the review inclusion criteria, were included (Table 1). Two reviewers (PO'R & SR) were involved in the data extraction of the final included studies.

Table 1

### 3. Critical appraisal of the evidence:

The six studies were critically appraised and screened using the Critical Appraisal Skills Programme (CASP).<sup>32</sup> Two of the studies were qualitative and four were quantitative, two of which included a Doctoral thesis and a Masters thesis. CASP Qualitative Checklist and CASP Cohort Study Checklist were used respectively. Each paper was assigned a score; 0-20 for qualitative papers and 0-24 for the cohort study papers (Table 1) whereby answers 'yes'=2, 'can't tell'=1 and 'no'=0. Of the six studies, the CASP scores were as follows; 16 (n=1), 19 (n=1) and 20 (n=3) and one had a score of 24.

### 4. Interpreting and applying the results:

Data extraction was performed on the findings and results sections of the included studies. The original studies were re-read and compared with the data extract files for verification purposes and to identify any extraction errors. Data were then analysed, inductively using the steps outlined by Whittemore and Knaff<sup>29</sup> viz. data reduction, categorisation, data comparison, conclusion drawing (thematic development). To strengthen the data analysis process, the data were interpreted using Braun and Clarke<sup>33</sup> thematic framework analysis. Key words and statements were highlighted and formed initial codes, which were both descriptive, and interpretive.<sup>33</sup> To establish a broader level of meaning, codes were clustered together to form potential themes, thus ensuring that they were relevant in answering the review question.<sup>33</sup> Cross comparisons were made across themes to ensure consistency and rule out any duplication.<sup>33</sup> Six reviewers were involved in the data analysis stage (PO'R; CK; PM; ID; SR & BW).

## Results

At the first stage of screening, 33 full text articles were assessed for eligibility and 27 full text studies were excluded with reasons (Fig. 1). Six studies were included in the CAT. The included studies were; qualitative<sup>34, 35</sup> (n=2) and quantitative<sup>36-39</sup> (n= 4) (Table 1). Two of the studies were from the UK,<sup>34, 35</sup> two were from France<sup>36, 37</sup>, one was from Canada<sup>38</sup> and one was from South Africa.<sup>39</sup> Following analysis, two overarching themes were identified viz. 1) Impact of diagnosis for now and the future and 2) Living with the psychosocial impact. In each of these, two further subthemes were developed (Table 2). Quotations from the qualitative papers are presented in Table 2.

Table 2

### **Theme 1: Impact of diagnosis for now and the future**

HCPs' lack of information regarding SJS and TEN appeared to have caused stress and anger on those affected. Engaging in avoidance behaviour has been identified as one of the ways that individuals appear to cope with the incumbent stress from SJS or TEN.

#### *Sub-theme 1: Health Care Practitioners not Knowing - The Distress on Patients*

Patients described feeling distressed when they initially had symptoms of SJS or TEN and presented to their doctor/hospital. They often did not know what to expect in the 'here and now' and into the future, due in part to failures in diagnosing the condition. They eventually found out that they had this devastating disease and, whilst it would have a significant impact on their lives, the degree of information that they received from HCPs was minimal, leading to feelings of anger, confusion and a lack of trust in HCPs.<sup>34, 35</sup> They also expressed anger and regret that they were not listened to by the doctor, especially when they were providing the doctors with information that may have helped in the prevention of SJS or TEN and/or its diagnosis.<sup>34, 35</sup>

#### *Sub-theme 2: Minimising the risks*

Patients learned to deal with the stress and distress of being diagnosed with SJS or TEN in different ways. In the case of the observed data, coping with the condition frequently led to individuals, not only avoiding medications that may have given rise to SJS or TEN, but also in being suspicious of all medications. Consequently, the impact of the diagnosis led to long-term avoidance behaviour.<sup>34, 35</sup> Similarly, a study by Raspaud<sup>36</sup> highlighted that 11 out of 15 patients indicated that they had a fear of

taking medications. In the Dodiuk-Gad *et al.*<sup>38</sup> study with 17 participants, the questionnaire 'Impact of Events Scale-Revised'<sup>40</sup> was used to establish evidence of PTSD. One of the factors within the scale was avoidance and 47% of participants (n=8) were above the cut off score. One patient expressed that they not only had a fear of medication but also a fear of attending the doctor.<sup>34</sup>

## **Theme 2: Living with the psychosocial impact**

Individuals who experience SJS or TEN refer to it as being a traumatic event in their lives. The evidence suggests that the conditions have long lasting impact on the lives of those affected and their significant others.

### *Sub-theme 1: Living with the distress*

Patients, who experienced SJS or TEN, used language aligned to that of experiencing a traumatic event. As with research from those who have suffered PTSD, patients articulated that they sometimes experienced depression and flashbacks, constantly living with the fear that it may happen again.<sup>34, 35</sup>

They were physically stripped of their skin, which was an external manifestation of what was happening to them emotionally. One man described how he was still trying to cope with the trauma of the illness. He described being scarred in his mind as well as in his body.<sup>34</sup> Trauma was also a key finding of the papers which quantitatively assessed the impact of SJS or TEN. In the Dodiuk-Gad *et al.*<sup>38</sup> study, 71% (n=12) had scores indicating clinically significant psychological distress; 65% of participants (n=11) had symptoms of post-traumatic stress. In addition, 29% of participants (n=5) had total scores, consistent with 'clinical signs of possible PTSD'.<sup>38</sup> While many patients experienced psychological distress, anxiety or depression, only a small minority were assessed by a mental health professional during the period following diagnosis. Similarly, Raspaud<sup>36</sup> reported that following discharge with an initial diagnosis of TEN, 12 patients from a sample of 15, presented with anxiety, depression, irritability, insomnia and nightmares. Zitha<sup>39</sup> found that of 26 patients diagnosed with SJS, TEN or SJS-TEN overlap ((n=16), (n=7) (n=3), respectively), 11 had anxiety and 13 were depressed at 6 months, following initial diagnosis. Using the Hospital Anxiety Depression Scale (HADS)<sup>41</sup>, 42% of patients (n=11) presented with a comorbidity of anxiety and depression [median HADS score 15.3; IQR 0.75-19.25]. The Hefez *et al.*<sup>87</sup> study, with 31 participants, found that 23% of patients (n=7) with SJS or TEN showed PTSD at six months.

### *Sub-theme 2 – Impact on Self and Others*

The diagnosis of SJS or TEN not only affected all aspects of the patient's life but also their relationship with significant others. Living with SJS or TEN caused them to fear for the future, particularly in relation to protecting their children from the condition. As highlighted in Theme 1, patients were frequently left with many unanswered questions by HCPs; this posed many challenges. The future could feel uncertain and unsafe; difficulty in coping with this uncertainty was particularly challenging.<sup>35</sup>

A sense of loss and sadness was evident in some patients' descriptions, with one man reporting how the illness had a long-term impact on his relationship with his wife due to him not being able to enjoy sex.<sup>35</sup> Similarly, the misdiagnosis of SJS by a doctor led to stress and stigma, whereby a patient described being tested for every known sexually transmitted disease which affected her personal relationship.<sup>35</sup>

There is evidence from the data that SJS and TEN affected the individual's self-image and how others viewed them.<sup>35</sup> They were 'stripped bare' of their self-image and of their friends. One patient described the look of disgust on the face of those who visited him and described himself as a 'monster'.<sup>35</sup>

SJS and TEN affected all aspects of quality of life. Using the Dermatology Life Quality Index<sup>42</sup> Zitha<sup>39</sup> reported that at 6 months, following initial diagnosis, the quality of life of 53% of patients (n=14) diagnosed with SJS or TEN or SJS-TEN overlap was moderately to extremely affected. Raspaud<sup>36</sup> referred to the medical file of one patient where it was noted that there was a repercussion on the patient's socio-professional and personal life, a restriction on their daily activity and an aesthetic discomfort. Dodiuk-Gad *et al.*<sup>38</sup> found 'major long-term, overlooked and treatable psychological complications and a decreased Health Related Quality of Life (HRQOL) among survivors, following a mean 51.6 +/-4.7 months (median 9, range 1–228) after SJS or TEN'. They also found that only 29% of participants (n=5) were employed following diagnosis. This was a common theme where Raspaud<sup>36</sup> also found that one third of participants (n=7) were in receipt of an allowance for adults with disabilities or disability compensation benefit. Patients highlighted that they had lost their job or had difficulty in getting one because of the condition.<sup>35</sup>

## **Discussion**



Empirical literature, exploring SJS and TEN, is predominately focused on the concomitant care, management and physical sequelae related to the conditions. There is a paucity of studies focused solely on the psychological consequences and on the impact of the conditions on patients' lives. Our CAT has identified six studies exploring the psychological impact of SJS and TEN and has revealed limited evidence. This lack of research may be attributed to the rarity of the disorder.

The available evidence suggests that SJS and TEN have a psychological impact which may have lasting implications on the quality of life of those affected and their significant others. Some patients were left feeling distressed with symptoms aligned to PTSD, anxiety and depression. Patients revealed that they were confused and unaware of how it was going to affect their lives from the time of diagnosis onwards, which could also negatively impact their relationships with significant others. Patient accounts identified a lack of knowledge on the part of the HCPs around the disorder. Consequently, patients were poorly informed. Following discharge from hospital, individuals expressed fear around taking medication and in attending their doctor and, subsequently, engaged in avoidance behaviour.

Many experts in the area have highlighted the importance of managing, researching and preventing the psychological sequelae in patients with SJS and TEN.<sup>13, 16, 25, 43</sup> Although some evidence exists, more clarity and research are required regarding the impacts on individuals' lives.<sup>25</sup> Eckert *et al.*<sup>44</sup>, in a meeting abstract, have documented the importance of HCPs putting strategies (not identified) in place to prevent the possible psychological sequelae such as PTSD in patients with SJS and TEN.

Patients with SJS or TEN are considered a similar cohort to burns patients in terms of experiencing a traumatic event. Identifying how the psychological care is managed with burns patients may be beneficial in the development of psychological support strategies for patients with SJS and TEN. Evidence has highlighted that there is a very close link between PTSD and the use of avoidance coping behaviours in burns patients and traumatised patients, which can affect recovery from the traumatic event.<sup>45-47</sup> Renneberg *et al.*<sup>48</sup> have proposed the implementation of routine screening of psychological distress and the ability to cope in burns patients. In addition, hypnosis, distraction techniques and relaxation therapy are some supportive interventions used with such patients in managing pain and psychological concerns<sup>49, 50</sup>; this may be relevant to patients with SJS and TEN.

Whilst the rarity of SJS and TEN poses research challenges,<sup>14</sup> particularly in terms of participants, it is an opportunity to commence research dialogue on a global front, so as to address such anomalies. This approach has been adopted by the International Rare Diseases Research Consortium.<sup>51</sup>

### **Clinical Message**

We conclude there is limited evidence detailing how best to minimise the psychological impact of SJS and TEN on patients. More research is required to address how best psychological care should be incorporated into the patient's supportive care plan.

Our patient was cared for in the ICU by a multidisciplinary team, encompassing the expertise of the dermatological team and the ICU specialists. This provided reassurance to both the patient and their family. In light of the findings from our CAT we took the following actions which should be considered in reducing the psychological impact on patients presenting with SJS or TEN.

- Patients have a right to information regarding their condition and the provision of it should allay some potential stresses. It is crucial to have meaningful patient involvement, from the onset, so as to ensure that their experiences inform decision-making and care pathways.
- HCPs need to be aware of SJS and TEN to assist in early patient diagnosis. Lack of awareness and information from HCPs has caused stress and anxiety for patients. Using education and training to increase HCP awareness and knowledge concerning SJS and TEN should facilitate their capacity to provide information, support or referral opportunities to patients and family members, thereby reducing anxiety whilst increasing satisfaction with care.
- The patient's care environment needs to be as stress free and person centred as possible.
- On discharge, a follow up appointment with the relevant HCP, such as a psychologist psychotherapist and/or social worker, should be considered so as to reduce the possibility of PTSD occurring.

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### Supporting information

Additional supporting information may be found in the online version of this article at the publisher's website:

Table S1 MEDLINE search strategy

**Table 1 Characteristics of included studies**

| Author                             | Year | Country | Aim/Purpose  | Type                            | Study Participants  | Key Message  | CASP  |
|------------------------------------|------|---------|--|---------------------------------|---|--|-------|
| Butt <i>et al.</i> , <sup>34</sup> | 2011 | UK      | To explore the experiences and beliefs of patients who had SJS/TEN and how these influenced their attitudes towards medicines and adverse drug reactions (ADRs). | Retrospective Qualitative Study | n=14 participants (n=8 female/n=6 male) Age range 21-82 years.<br><br>Direct quotes from interviews referenced in Table 2 as 'patient n'.     | Life threatening ADRs such as SJS and TEN may continue to affect patients' lives long after the event having an impact on their current lives physically and psychologically. Patients can lose trust in healthcare professionals and in medicines in general.                     | 19/20 |
| Butt <i>et al.</i> , <sup>35</sup> | 2012 | UK      | To illuminate patient experiences of SJS and TEN by analysing unsolicited internet narratives or postings of those who have had                                  | Qualitative Study               | n=208 internet descriptions (n=128 female/n=68 male/n=12 unknown)<br><br>n=139 posts from those with direct experience of SJS/TEN and n=69 by | Patients and relatives with experience of SJS or TEN posted on support group websites to share their experiences, provide support to other sufferers and obtain advice from others with similar experiences. Findings indicted that patients and their relatives had many concerns | 20/20 |



|                                     |      |        |   |  |   |  |       |
|-------------------------------------|------|--------|---|--|---|--|-------|
|                                     |      |        | personal experience of drug induced SJS and TEN.  |  | relatives.<br><br>Direct quotes from posts referenced in Table 2 as 'internet description n'. | about the ADR often long after the event.  |       |
| Raspaud <sup>36</sup>               | 2014 | France | To describe the sequelae of SJS and TEN including impact on quality of life.  | Quantitative Descriptive Study - Doctoral Thesis | n=21 participants (n=18 female/n=3 male)  | SJS and TEN can cause long term sequelae including cutaneous (70%), psychological (60%) and ocular (45%) complications. Psychological sequelae are an important part of SJS and TEN complications and may be underestimated.                                       | 16/24 |
| Hefez <i>et al.</i> , <sup>37</sup> | 2018 | France | To assess the prevalence of PTSD and its risk factors in a population of adults with SJS/TEN who had benefited from early psychological | Moncentric Prospective Study                     | n=31 patients (n=19 female/n=12 male)   | Despite frequent prescription of hydroxyzine at the acute phase, almost one quarter (23%) of patients with SJS/TEN had PTSD at 6 months. A systematic psychiatric evaluation should be offered regularly for at least 1 year after the acute phase of the disease. | 24/24 |

|  |      |              |   |                    |   |  |       |
|--|------|--------------|---|--------------------|---|--|-------|
|  |      |              | evaluation.   |                    |   |  |       |
| Dodiuk-Gad <i>et al.</i> , <sup>38</sup> | 2016 | Canada       | To explore the long-term psychological complications and Health Related Quality of Life (HRQOL) of SJS/TEN survivors.   | Quantitative Study | n=17 participants (n=11 female/n=6 male)  | Survivors of SJS/TEN had major long-term, overlooked and treatable psychological complications and decreased HRQOL following a mean $51.6 \pm 74.7$ months (median 9, range 1–228) after SJS/TEN. Psychological support during hospitalization, prior to discharge and throughout follow up should be offered to all patients. | 20/24 |
| Zitha <sup>39</sup>                      | 2015 | South Africa | To prospectively investigate the presence of anxiety and depression in patients with severe cutaneous adverse drug reactions (SCADR), as well as assess their | Quantitative Study | n=48 participants (n=35 female/n=13 male)<br><br>n=34 participants were diagnosed with SJS, TEN or SJS-TEN overlap. | There is a high prevalence of anxiety and depression among patients with SJS/TEN and the disease negatively affects quality of life. At 6 weeks post diagnosis 13/34 patients with SJS/TEN had both anxiety and depression while at 6 months 11/26 were cases of comorbid anxiety and depression. At 6 months the quality      | 20/24 |

|  |  |  |   |  |  |   |  |
|--|--|--|---|--|--|---|--|
|  |  |  | quality of life at two time intervals, using validated scoring systems. |  |  | of life of 14/26 patients was moderately to extremely affected. |  |
|--|--|--|---|--|--|---|--|

**Table 2: Themes, subthemes and representative quotes from qualitative papers<sup>34, 35</sup>**

| Theme   | Subtheme  | Representative quotes  |
|---|---|--|
| 1. Impact of diagnosis for now and the future | 1. Health Care Practitioners not knowing – the distress on patients | <p><i>"Well, I'd never heard of it, and when the doctors themselves didn't know anything about it, it was all a bit scary ..."</i> (Patient 1)<sup>34</sup></p> <p><i>"I definitely feel that the medical profession is not aware enough of Stevens-Johnson."</i> (Internet description 195)<sup>35</sup></p> <p><i>"I was amazed at the lack of knowledge on the part of the medical professionals. I clearly knew more about this disorder than anyone else I dealt with"</i> (Internet description 67)<sup>35</sup></p> <p><i>"... the doctor diagnosed me with things like chicken pox, measles, and flea bites ..."</i> (Internet description 136)<sup>35</sup></p> <p><i>"... my mom looked frantically through a book of medical problems and came to Steven Johnsons Syndrome. It fit the description perfectly but when she asked the doctor if it could be that he said no, it's too rare ..."</i> (Internet description 136)<sup>35</sup></p> <p><i>"I'm totally clueless about SJS though. Am I now a carrier? I'm aware of the fact it was due to an allergic reaction to the drugs prescribed to me. I think I was extremely lucky as it only affected my mouth and not the rest of my body... Could</i></p> |

anyone update me on what happens now with regards to SJS and me being a carrier? I'm aware I shouldn't use that medicine ever again" (Internet description 216)<sup>35</sup>

"Well I felt bitter that I should not have been given cefalexin, but it was on my notes it said I'm allergic to penicillin ... and there is a train of thought that cefalexin is closely related to penicillin, and she [the GP] shouldn't have given me that knowing my history, all my notes say no penicillin .... I feel she [the GP] should have looked it up on the Internet, she's got the means, she should have inquired rather than handing out willy-nilly ..." (Patient 4)<sup>34</sup>

"But the only thing now is, it's made me so scared of taking pills.... I won't go to the doctors if I can help it now ... um, you know if you got infections or anything like that, I won't go, and if I had to go, was forced to go, he gives me tablets, I ask him ... I must be the worst person, the worst nightmare they've had! [smiles] ... I ask him, then I ask the chemist [laughs], then I think, I'm not taking them! Just in case, you know? It's frightening ..." (Patient 1)<sup>34</sup>

"I am still quite confused by this syndrome. Will it stay in her system forever? Since it is a syndrome, does it always come back and never go away? I don't know anymore and I am scared for my daughter, please help." (Internet description 71)<sup>35</sup>

|  |                             |  |
|--|-----------------------------|--|
|  |                             |  |
|  | 2. Minimising the risks     | <p><i>'I stopped taking any medication unnecessarily, like paracetamol, penicillin, Nurofen®, and ... Locketts® [medicated lozenges], because they're like medicated inside aren't they ... and, so I stopped taking all that kind of stuff... and I get really bad migraines as well, that will actually make me throw up, but I still don't take Nurofen®.... because of the chance ...' (Patient 7)<sup>34</sup></i></p> <p><i>'I think it's just made me aware of everything really ... um, if er, if new sweets have come on [to the market] or anything ... from different foods, you think, knowing that it's stupid! But it does ... you think about it!' (Patient 1)<sup>34</sup></i></p> <p><i>"... in the meantime, we live one day at a time, suspicious of all meds, suspicious of all foods, and even suspicious of the air that James breathes ... why, why, why???" (Internet description 92)<sup>35</sup></i></p> |
| 2. Living with the psychosocial impact | 1. Living with the distress | <p><i>"Yes ... being depressed, yes, because as I said I get flashbacks, your memory goes but you remember certain things like when I'm having a shower or taking my top off or look in the mirror it all comes back again." (Patient 13)<sup>34</sup></i></p> <p><i>"I will never forget. I feel traumatized and sometimes I feel very afraid that this might happen again." (Internet description 34)<sup>35</sup></i></p>   |

|  |  |   |
|--|--|---|
|  |  | <p><i>“Yes because I'm scarred in my mind as well as scarred on my body ... I have flashbacks to my illness ... the doctors were great and the hospital was great ... but what let me down was the aftercare because ok, I got home and had to go back for checkups, but I said what about my scars? And the doctor was great he said you're a big strong lad, you'll be able to cope, but really I don't.” (Patient 13)<sup>34</sup></i></p> |
|  |  |   |

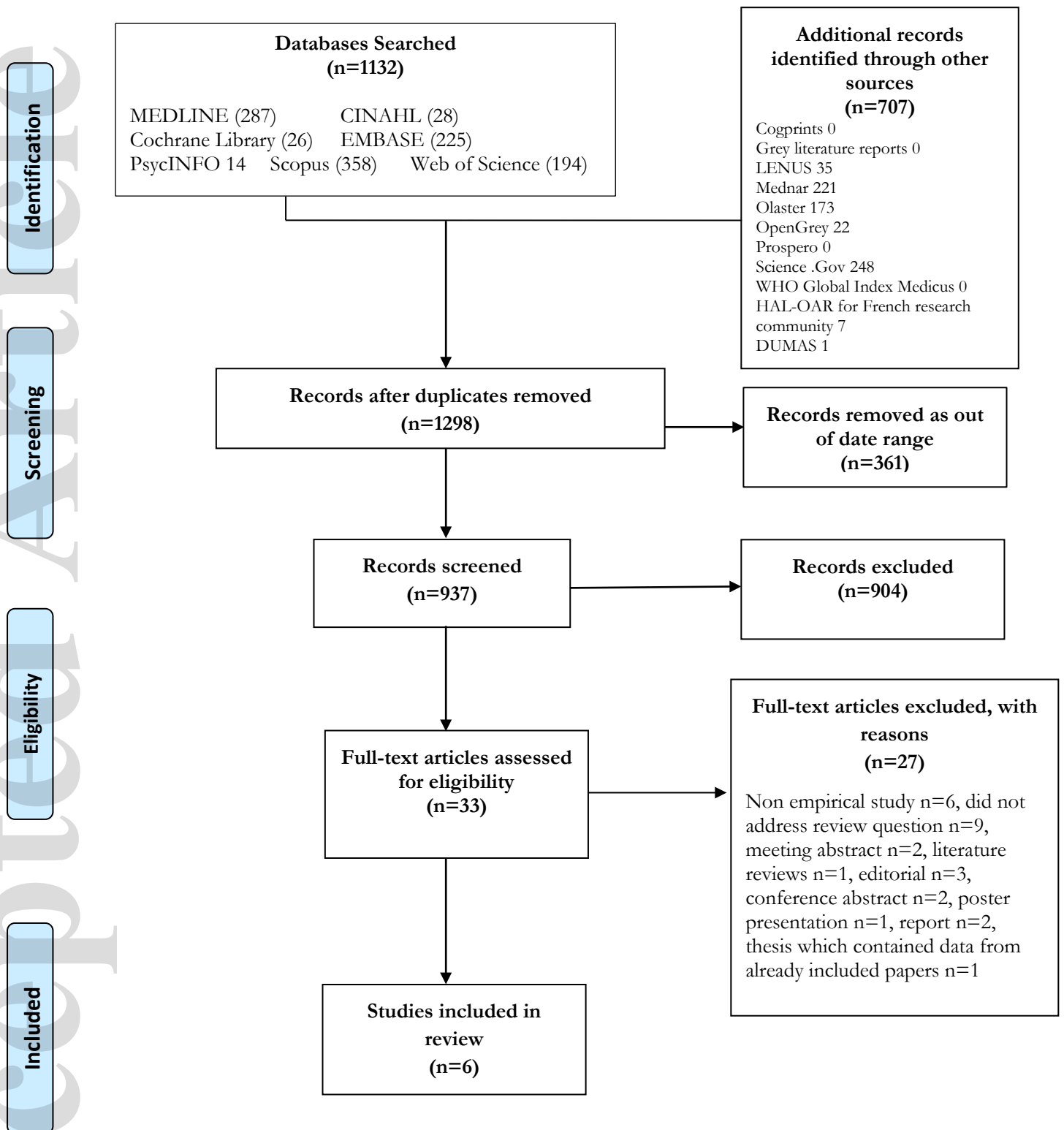


Fig 1: PRISMA flow diagram<sup>30</sup>