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Clinical science

Attribution of neuropsychiatric symptoms and prioritization of evidence in the diagnosis of neuropsychiatric lupus: mixed methods analysis of patient and clinician perspectives from the international INSPIRE study

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Abstract

Objective: Neuropsychiatric lupus (NPSLE) is challenging to diagnose. Many neuropsychiatric symptoms, such as headache and hallucinations, cannot be verified by tests or clinician assessment. We investigated prioritizations of methods for diagnosing NPSLE and attributional views.

Methods: Thematic and comparative analyses were used to investigate how clinicians prioritize sources of evidence from a 13-item list, and explore discordances in clinician (surveys $n = 400$, interviews $n = 50$) and patient (surveys $n = 676$, interviews $n = 27$) perspectives on attribution.

Results: We identified high levels of variability and uncertainty in clinicians' assessments of neuropsychiatric symptoms in SLE patients. In attributional decisions, clinicians ranked clinicians' assessments above diagnostic tests (many of which they reported were often unenlightening in NPSLE). Clinicians ranked patient opinion of disease activity last, and 46% of patients reported never/rarely having been asked if their SLE was flaring, despite experienced patients often having 'attributional insight'. SLE patients estimated higher attributability of neuropsychiatric symptoms to the direct effects of SLE on the nervous system than clinicians ($P < 0.001$ for all symptoms excluding mania), and 24% reported that their self-assessment of disease activity was never/rarely concordant with their clinicians. Reports of misattributions were common, particularly of non-verifiable diffuse symptoms. Terminology differed between clinicians and influenced attribution estimates.

Conclusion: NPSLE diagnostic tests and clinician assessments have numerous limitations, particularly in detecting diffuse neuropsychiatric symptoms that can be directly attributable and benefit from immunosuppression. Our findings suggest that incorporating patient attributional insights—although also subject to limitations—may improve attribution decision-making. Consensus regarding terminology and interpretations of 'direct attributability' is required.

Keywords: neuropsychiatric lupus, SLE, NPSLE, CNS lupus, patient-clinician interactions, attribution, misattribution, diagnosis, diagnostic tools, attribution.

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Rheumatology key messages

- There is high variation in attributional views and estimates, and lack of consensus in terminology.
- Clinicians prioritized assessment tools for neuropsychiatric lupus in the following order: clinician assessment>diagnostic tests>patient reports/views.
- Valuing patient attributional insights may improve NPSLE/NPSLE flare attribution decision-making, particularly regarding diffuse neuropsychiatric symptoms.

Introduction

Nervous system involvement remains a major diagnostic and therapeutic challenge in systemic lupus erythematosus (SLE) [1, 2]. A principal difficulty is differentiating neuropsychiatric SLE (NPSLE)—involving the direct effects of SLE on the nervous system [1]—from symptoms arising from the treatments and the indirect effects of the challenges of living with an unpredictable chronic disease [2], or from co-occurring pathologies that are largely or wholly unrelated to SLE or its treatment. The attributional difficulties are in part the result of neuropsychiatric symptoms being frequently non-specific [3], and some—such as cognitive dysfunction and headaches—being common in the general population [4]. There is no unifying model to explain the pathogenesis of NPSLE and, despite numerous research studies, there is no 'gold standard' diagnostic test [4], and diffuse nervous system involvement is often undetectable with existing serological, electrophysiological and imaging investigations [3]. These difficulties are further compounded by a high degree of patient reticence in reporting NP symptoms, and the under-estimation of potential NP symptom range and prevalence in SLE by clinicians [5]. It is therefore not surprising that doubts have been raised about clinician judgement being used as the 'gold standard', particularly for subjective symptoms [5, 6].

Difficulties in correctly attributing neuropsychiatric symptoms in patients with undiagnosed SLE adds to delays in SLE diagnosis and treatment, and contributes to an increase in disease-related damage [7]. NPSLE diagnostic difficulties and delays also have serious consequences post SLE diagnosis, including increased morbidity and mortality [8]. Misattributions can entail both under and over attributing to a direct disease effect [7, 9], lead to inappropriate treatment [10] and generate long-term distrust in clinicians [11]. There is therefore an imperative to identify and correctly attribute NP symptoms at an early stage in the clinical assessment of patients with SLE. This imperative, along with the continued centrality of clinician judgement in NP symptoms attribution, suggests the need to better understand these clinician attribution processes and the potential role of patients. There have been important NPSLE studies [4, 12] and attribution guidelines [1, 6] in recent years. However, no research to date has ascertained and compared SLE patient and clinician views of the attribution of neuropsychiatric symptoms, or investigated the acceptability and prioritization of methods used in diagnosing NPSLE/NPSLE flares in everyday practice in a range of clinician specialities. The objective of this study was to explore these attributional views and diagnostic method priorities, in order to identify potential areas for improvement from both clinician and patient perspectives.

Methods

INSPIRE Project

This study is part of the INSPIRE (Investigating Neuropsychiatric Symptom Prevalence and Impact in Rheumatology Patient Experiences) research project which incorporates inter-linked studies exploring different aspects of neuropsychiatric symptoms, and commenced with identifying the self-reported prevalence of 30 potential NP symptoms [5]. Mixed methods are used to complement the respective methodological strengths [13].

Due to most symptoms having multiple potential aetiologies, study inclusion was on pragmatic and/or phenomenological grounds (e.g. classifying as neuropsychiatric to distinguish from dermatological, musculoskeletal or respiratory symptom groupings, for example), and following extensive pre-survey consultation with patients and clinicians rather than to represent any fixed notion of aetiology or mechanism.

In designing the study, we used symptoms and descriptions as opposed to diagnoses wherever possible. For example, 'very low mood' rather than 'depression', and 'delusions and/or paranoia' as opposed to (possible) 'psychosis'. This was to enable more comparability between patients and clinicians by using the same terms, and by focusing on descriptions. This also reduces inaccuracies from the current level of underdiagnoses, potential misdiagnoses, and potential for patient (mis) self-diagnoses. In a few cases (e.g. anxiety) the description was the same as the diagnosis due to the diagnostic term also being the most commonly used lay descriptive term.

Although the inclusion of fatigue was debated due its aetiology being likely highly heterogeneous, and it being excluded from previous NPSLE guidelines and algorithms [1, 14, 15], justifications for inclusion were: (i) it is increasingly pragmatically classified as a neuropsychiatric symptom in other research into complex multi-system conditions, such as long-Covid [16]; (ii) it is the most impactful systemic autoimmune rheumatic disease (SARD) manifestation [17], and therefore any additional evidence as to level of direct/indirect attributability could be of great value in determining the best treatment; and (iii) consultations with patients during study design revealed a strong preference for its inclusion.

Participants and design

International recruitment was conducted in 2022 via social media, patient support groups and professional networks, using the online survey instrument Qualtrics. A shorter survey targeting specific groups under-represented in the first survey responses (ethnic minority and male patients, and neurology

clinicians) was made available online in 2023. All patients had to be 18 years or over, and report a diagnosis of SLE confirmed on clinical correspondence. Clinicians were excluded if they were below the level of specialist trainee.

Clinicians were requested to rank their top and bottom three methods used to assist in diagnosing NPSLE/NPSLE flares from a choice of 13 (Table 2). These methods were chosen based on existing attribution models [1], pre-survey interviews and INSPIRE team multidisciplinary input. They included diagnostic tests such as brain imaging, clinician assessments and patient interpretations of level of disease activity. SLE patients and clinicians were asked for their views of level of attributability for symptoms [from 0 (no direct attributability) to 100 (symptom is completely attributable to the direct effect of lupus on the brain/nervous system)]. Patients were asked to assess the level of attributability in themselves for symptoms experienced >3 times in their lives, whilst clinicians were asked to estimate the mean level of direct attributability of all lupus patients with that symptom. Patients and clinicians were given six options (from never to always) for questions regarding reporting of symptoms, including being asked/asking if the SLE was flaring. Patients were asked to rate measures of satisfaction with care and life as a percentage.

Except in the case of exploratory pre-survey interviews, interviewees were purposively selected from survey respondents to ensure contributions from participants with a range of attributional views and socio-demographic characteristics, including age and ethnicity. Interviews (mostly via Zoom)—conducted by three experienced medical researchers—were audio recorded and transcribed verbatim.

Analysis

Following data cleaning, *t* tests and χ^2 tests were used to investigate the associations between variables of interest (including patient–clinician and inter-speciality variations). Correlations were calculated using Pearson's or Spearman's coefficient as appropriate. Statistical significance level (alpha) was $P = 0.05$. Qualitative analysis included data from interviews and open-ended survey questions. Stages of thematic analysis [14, 15] included: (i) full immersion in the data; (ii) developing a coding scheme, and subsequent coding; (iii) combining participant transcript extracts for codes; and (iv) the study team discussing and generating themes directly from the data. Triangulation of qualitative and quantitative results, participant checking of initial results [16], and discussion of conflicting views reduced threats to validity. In-depth descriptions of methods are included in Supplementary Data S1, available at *Rheumatology* online.

Ethical approval

The Cambridge Psychology Research Committee provided ethical approval: PRE 2022.027. Informed consent was taken electronically on surveys and verbally (audio recorded) for interviews. The pre-registered protocol and statistical analysis plan can be found at: https://osf.io/zrehm.

Results

Clinician participants ($n = 400$, 51% rheumatologists, 52% female) were practising in a broad range of countries (Table 1). Patients ($n = 676$) were mainly female (94%), and white (80%), and 65% had been diagnosed for >5 years. Interviews were conducted with 50 clinicians and 27 patients. We have described as 'directly attributable' those symptoms that participants attributed to the direct effects of SLE on the brain/nervous system.

Four main themes were identified. Theme 1: Symptom attributions: frequencies, confidence and concordance. Theme 2: Hierarchies of evidence in diagnosing NPSLE. Theme 3: Consequences of misattributions and the contested role of co-diagnoses. Theme 4: Patient reporting and attributional insight.

Theme 1: Symptom attributions: frequencies, confidence and concordance

Clinicians openly acknowledged limited collective and individual knowledge of the pathogenesis of NPSLE, with a typical response being: '*we don't know enough*' (multiple clinicians). The mean number of NP symptoms (from the 30 listed in the survey) patients reported having ever experienced was 14 (SD 6). Reliably attributing each symptom to one of the many, often inter-related, potential causes was reported to be extremely challenging for clinicians and patients:

> '*Any patient with neuropsychiatric lupus would almost always have multiple symptoms, frequently some are psychiatric and some are neurological, and they exist in a kind of mess, and chronologically they didn't start on the same day* … [need to] *work out, is it lupus disease activity, is it the medication, is it the experience of having been a lupus patient for many years and the medical profession and the family, or is it totally incidental.*' (Ppt 51, psychiatrist, England)

Patient estimates of the proportion of their symptoms that were directly attributable were higher than clinician estimates for SLE patients as a whole for all symptoms ($P < 0.001$ aside from mania) (Fig. 1). There was considerable variation between individual clinician estimates (Fig. 2). Fatigue was estimated as the most directly attributable symptom by patients (mean 93% direct attributability, SD 14) and clinicians (mean 59%, SD 29). In general, psychiatrists estimated most symptoms as being more directly attributable to NPSLE activity than other clinicians; while neurologists had the lowest estimates (Fig. 1B), with notable exceptions including hallucinations and mania (mean direct attribution rating of 60% for mania for neurology respondents, compared with 35% for rheumatologists, $P < 0.001$).

Reported levels of confidence in diagnosing NPSLE ranged from 0–100 (%), with a mean of 49 (SD 28.1), and varied significantly between clinicians from different countries, gender and specialities (Fig. 3A). Clinicians practising in Latin America, neurologists and males reported the highest level of confidence [for example, male clinician confidence was 55 *vs* female confidence of 45 (CIs of mean difference=3.63–17.25, $P = 0.03$)]. There was a weak positive correlation ($r = 0.22$, $P < 0.001$) between clinician age and confidence.

There were significant differences ($P < 0.001$) between patient and clinician views as to concordance in assessment of disease activity (Fig. 3B). Although 69% of clinicians and 43% of patients perceived that they were often, usually, or always in agreement (Fig. 3C), 24% of patients felt their self-assessments were never/rarely in agreement with their clinicians, and 46% of patients reported never/rarely being asked

Table 1. Participant characteristics

Characteristic	Patient survey ($n = 676$) (%)	Patient interviews ($n = 27$) (%)	Clinician survey ($n = 400$)(%)	Clinician interviews ($n = 50$)(%)
Age				
18–30	58 (9%)	3 (11%)	16 (4%)	0
30–39	112 (17%)	3 (11%)	135 (34%)	11 (22%)
40–49	159 (24%)	8 (30%)	135 (34%)	19 (38%)
50–59	191 (28%)	8 (30%)	69 (17%)	12 (24%)
60–69 (60+ for clinicians)	109 (16%)	3 (11%)	45 (11%)	8 (16%)
70+	43 (6%)	2 (7%)	N/A	N/A
Prefer not to say	4 (<1%)	0 (0%)	0 (0%)	0 (0%)
Gender				
Female	634 (94%)	22 (81%)	209 (52%)	23 (46%)
Male	38 (6%)	5 (19%)	186 (47%)	27 (54%)
Other/undisclosed	4 (<1%)	0 (0%)	5 (1%)	0 (0%)
Country/region				
England	434 (64%)	9 (33%)	156 (39%)	28 (56%)
Scotland	48 (7%)	4 (15%)	16 (4%)	2 (4%)
Wales	32 (5%)	4 (15%)	6 (2%)	2 (4%)
N. Ireland or Republic of Ireland	15 (2%)	2 (7%)	2 (<1%)	0 (0%)
US or Canada	15 (2%)	2 (7%)	65 (16%)	4 (8%)
Europe	97 (14%)	2 (7%)	68 (17%)	6 (12%)
Asia	19 (3%)	2 (7%)	34 (9%)	3 (6%)
Latin America	2 (<1%)	0 (0%)	30 (8%)	4 (8%)
Australia or New Zealand	5 (<1%)	1 (4%)	10 (3%)	0 (0%)
Other	9 (2%)	1 (4%)	13 (3%)	1 (2%)
Ethnicity			Not recorded	Not recorded
White	542 (80%)	15 (56%)		
Asian	54 (8%)	6 (22%)		
Black	37 (5%)	4 (15%)		
Mixed	30 (4%)	2 (7%)		
Other/	10 (1%)	0 (0%)		
Undisclosed	3 (<1%)			
Time since diagnosis			N/A	N/A
<1 year	38 (6%)			
1–2 years	82 (12%)			
3–5 years	113 (17%)			
6–9 years	119 (18%)			
10 years +	321 (47%)			
Unsure or undisclosed	3 (<1%)			
Clinician specialty	N/A	N/A		
Rheumatology			204 (51%)	21 (42%)
Psychiatry			96 (24%)	8 (16%)
Neurology			52 (13%)	10 (20%)
GP/Primary care			11 (3%)	5 (10%)
Other			37 (7%)	6 (12%)
Clinician post	N/A	N/A		
Consultant/senior GP			277 (69%)	34 (68%)
Registrar/junior GP			75 (19%)	10 (20%)
Nurse			20 (5%)	4 (8%)
Other/undisclosed			28 (7%)	2 (4%)

their view as to whether their SLE was flaring (Fig. 3D). Many patients detailed situations where they felt their symptom reporting or self-interpretations had been treated with a lack of respect and/or credulity, leading to distrust, persisting psychological damage, and perceptions of misattributions:

> '*When I enter a medical appointment and my body is being treated as if I don't have any authority over it and what I'm feeling isn't valid then that is a very unsafe environment … You are giving up control over your own body, and I'll tell them my symptoms and they'll tell me that symptom is wrong, or I can't feel pain there, or in that way … The entire thing has been so protracted, and degrading and dehumanising … If I had continued to have regard for clinicians' expertise over mine, I would be dead.*' (Ppt 1159, Ireland)

Theme 2: Hierarchies of evidence in diagnosing NPSLE/NPSLE flares

The three assessment methods ranked by clinicians as the most important in diagnosing NPSLE/NPSLE flares (%s indicate proportion of clinicians who ranked method in their top 3) (Table 2) were: (i) clinician assessment of patient's presentation (44.7%); (ii) presence of other disease manifestations (39.2%); and (iii) abnormal brain imaging (38.8%). The three assessment items ranked as least important were: asking the patient their view as to whether their SLE is flaring (ranked in

Table 2. Clinician rankings of assessment methods for diagnosing NPSLE/NPSLE flares

Assessment method	MOST important evidence for diagnosis decisions % ranking in TOP 3 for each category				Assessment method	LEAST important evidence for diagnosis decisions % ranking in BOTTOM 3 for each category			
	Total	Rheum	Psych	Neuro		Total	Rheum	Psych	Neuro
Clinician assessment of patient's presentation [1]	**44.7**	**44.8**	**40.7**	**51.4**	Asking patient view if SLE flaring [12]	**48.1**	**54.1**	18.5	**62.2**
Presence of other disease manifestations [2]	**39.2**	**43.1**	**33.3**	24.3	Reduced complement [10]	**37.8**	**35.4**	**61.1**	10.8
Abnormal brain imaging [3]	**38.8**	**43.6**	20.4	**56.8**	Raised autoantibodies [6]	**35.7**	**38.1**	**27.8**	**37.8**
Response to treatment (inc. improvement on steroids) [4]	34.0	35.4	24.1	**35.1**	Other objective tests (e.g. EEG, EMG) [11]	29.6	24.3	**41.5**	**24.3**
Comparison of Pt behaviour and cognition from usual [5]	25.4	26.5	**29.6**	16.2	Eliciting details from family/friends [9]	25.8	27.1	25.9	24.3
Raised autoantibodies (such as anti dsDNA) [6]	20.6	18.2	24.1	24.3	Presence of other disease manifestations [2]	20.3	21.5	18.5	18.9
Eliciting Pt details of symptoms [7]	16.2	14.4	24.1	8.1	Neurological examination [8]	19.6	19.3	18.9	22.2
Neurological examination [8]	14.1	13.3	18.5	5.4	Eliciting Pt details of symptoms [7]	16.5	19.3	7.4	10.8
Eliciting details from family/friends [9]	11.7	9.9	18.5	13.5	Abnormal brain imaging [3]	15.8	13.8	22.2	10.8
Reduced complement [10]	10.7	10.5	5.6	24.3	Comparison of Pt behaviour and cognition from usual [5]	15.5	17.7	7.4	13.5
Other objective tests (e.g. EEG, EMG) [11]	10.7	12.7	3.8	13.9	Response to treatment [4]	9.3	8.3	14.8	10.8
Asking patient view if SLE flaring [12]	3.8	2.2	11.1	0	Clinician assessment of patient's presentation [1]	5.2	4.9	1.9	10.8

$N = 291$ total, including: Rheumatology ($N = 181$), Psychiatry ($N = 54$), Neurology ($N = 37$) and 19 clinicians from other specialities. The top three overall and by speciality are highlighted in **bold.** Note: An additional measure 'seeking expert opinion' was included in the survey but excluded from the results as the rankings were largely dependent on clinician seniority.

the bottom three by 48.1%, and in the top three by 3.8%, of clinicians), and the two most commonly used blood measures of disease activity: complement and autoantibodies such as anti dsDNA. The anticipated direct inverse relationship between the orders in the highest and lowest priorities columns was not observed for all the assessment modalities. This was particularly evident in the case of elevated autoantibodies, which achieved a top-three ranking from 20.6% of clinicians whilst also being positioned in the bottom three by 35.7% of clinicians (Fig. 4). This was discussed in clinician interviews where a typical response from lupus specialists was that: '*Sensitivity of antibodies in neuropsychiatric lupus is so low that it is not helpful in diagnosis*' (Ppt 24, rheumatologist, England), but they felt that less experienced clinicians may be overly reliant on '*outdated*' (several clinicians) literature and ACR guidelines.

Grouping the assessment tools into three categories, clinicians overall (and rheumatologists when divided by specialities) ranked them in the following descending order of importance: clinicians' assessments (calculated as the mean of items 1, 2, 5 and 8 in Table 2), diagnostic test results (mean of items 3, 6, 10 and 11), followed by patient reports (mean of items 7 and 12). Rankings, however, varied by speciality, with neurologists ranking diagnostic tests first and patient reports last, and psychiatrists ranking in the order of: clinician assessments>patient reports>diagnostic tests. Although most clinicians stated that diagnostic tests were often normal, their importance in excluding alternative aetiologies was frequently highlighted: '*Objective testing is absolutely essential as it often excludes other causes such as other neurological disease, infection, tumours . . .*' (Ppt 190, rheumatologist, USA)

There were significant differences between specialities in the value given to some assessment instruments, with the most notable differences being 62% of neurologists valuing patients' opinions of disease activity in the bottom three, compared with 19% of psychiatrists, and psychiatrists placing a lower value on complement testing and brain imaging than other specialities. Patients frequently shared the viewpoint that: '*Medics rely on results and machines more than what the actual patient states*' (Ppt 44, Scotland).

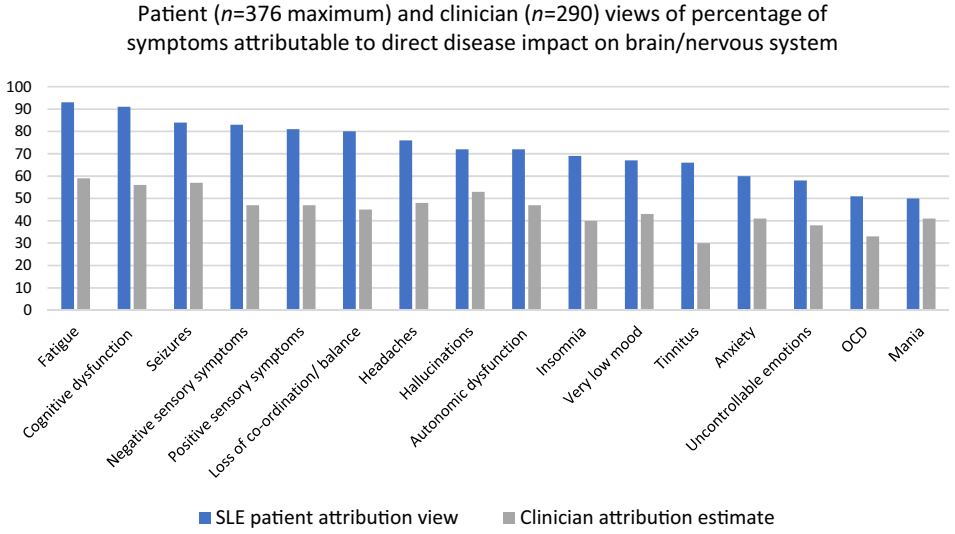
Sub-theme: Diagnostic test results provide verification, validation and vindication, yet are '*often unenlightening*'

The majority of non-rheumatology clinicians (64% of neurology and 81% of psychiatry participants) reviewed <5 SLE patients per year, and may have had less opportunity to develop the '*gut feeling* [and] *pattern recognition*' (Ppt 27, rheumatologist, England) several lupus specialists indicated they used in diagnosing NPSLE. Clinicians and patients desired objective evidence of symptoms, so as to provide additional confidence in what were considered highly challenging diagnostic and treatment decisions:

> *'I never know. It is more my past experiences and the "art of medicine" that guide me. When we are lucky enough to get objective data to support a diagnosis of NPSLE [like] an abnormal CSF it does improve my confidence level, as does treatment response, but all of our tools are woefully inadequate'.* (Ppt 212, rheumatologist, USA)

Diagnostic tests provided verification of clinician assessments, and so helped to inform potentially harmful treatment regimens; and validation for patients that their symptoms were 'real'. They also provided vindication in some cases where the patient had felt their subjective

A



B

Mean percentage of symptoms considered directly attributable by group.					
	SLE patients *n*=376 (max) % (SD)	All clinician *n*=290 % (SD)	Rheum *n*=190 % (SD)	Psych *n*=60 % (SD)	Neurologists *n*=40 % (SD)
Fatigue	93 (14.0)	59 (28.7)	59 (29.6)	67 (24.5)	45 (25.3)
Cognitive dysfunction	91 (15.1)	56 (27.3)	56 (28.4)	62 (22.7)	46 (24.7)
Weakness	88 (18.4)				
Seizures	84 (30.3)	57 (33.0)	56 (34.1)	59 (27.4)	66 (30.4)
Negative sensory symptoms	83 (22.9)	47 (29.8)	42 (30.2)	61 (24.6)	45 (26.1)
Hypersensitivity	81 (26.7)				
Positive sensory symptoms	81 (24.7)	47 (29.3)	43 (29.7)	63 (22.4)	43 (27.0)
Loss of co-ordination/ balance	80 (25.3)	45 (29.6)	40 (30.1)	63 (23.5)	42 (23.6)
Difficulty swallowing	79 (27.1)				
Headaches	76 (25.7)	48 (29.8)	49 (31.9)	54 (24.2)	39 (22.0)
Tremors	75 (30.5)				
Hallucinations	72 (29.9)	53 (33.9)	52 (34.8)	53 (31.9)	63 (29.1)
Autonomic dysfunction	72 (27.8)	47 (32.3)	44 (33.0)	60 (27.4)	41 (32.6)
Feeling of unreality	71 (27.1)				
Insomnia	69 (29.1)	40 (29.3)	35 (28.9)	63 (21.1)	30 (24.5)
Palpitations	69 (27.3)				
Restlessness	68 (27.6)				
Very low mood	67 (24.7)	43 (26.7)	40 (27.7)	56 (21.8)	37 (22.5)
Tinnitus	66 (35.5)	30 (27.7)	23 (24.7)	52 (29.1)	24 (18.9)
Bowel or bladder symptoms	66 (28.1)				
Delusions and/or paranoia	65 (30.8)				
Disrupted dreaming sleep	64 (29.9)				
Anxiety	60 (27.4)	41 (27.3)	38 (28.5)	53 (23.0)	32 (21.3)
Uncontrollable emotions	58 (30.3)	38 (30.3)	32 (29.2)	54 (30.3)	39 (27.0)
Obsessive compulsive disorder	51 (29.4)	33 (29.0)	29 (29.1)	49 (26.7)	33 (24.2)
Mania	50 (34.2)	41 (32.1)	35 (31.0)	52 (30.9)	60 (26.9)
Disinhibition	49 (36.0)				

Figure 1. Patient and clinician views on percentage of symptoms attributable to direct disease effect. Clinicians were only asked about a selection of symptoms so as to reduce the time burden (hence gaps in the table). Patients were only asked to estimate attribution of symptoms they had experienced >3 times in their lives

symptoms had been disbelieved. However, diagnostic tests were reported to be '*often unenlightening*' (Ppt 59, neurologist, England) (Fig. 4b), with comments including: '*it's mostly a pathological thing that ultimately you can see on a microscope on the brain, but only once they're dead*' (Ppt 12, neurologist, Scotland). Diagnostic tests, although often considered to be more accurate than assessments relying on human (both clinician and patient) subjectivities, also require human interpretation, introducing further inaccuracies to their already low sensitivity:

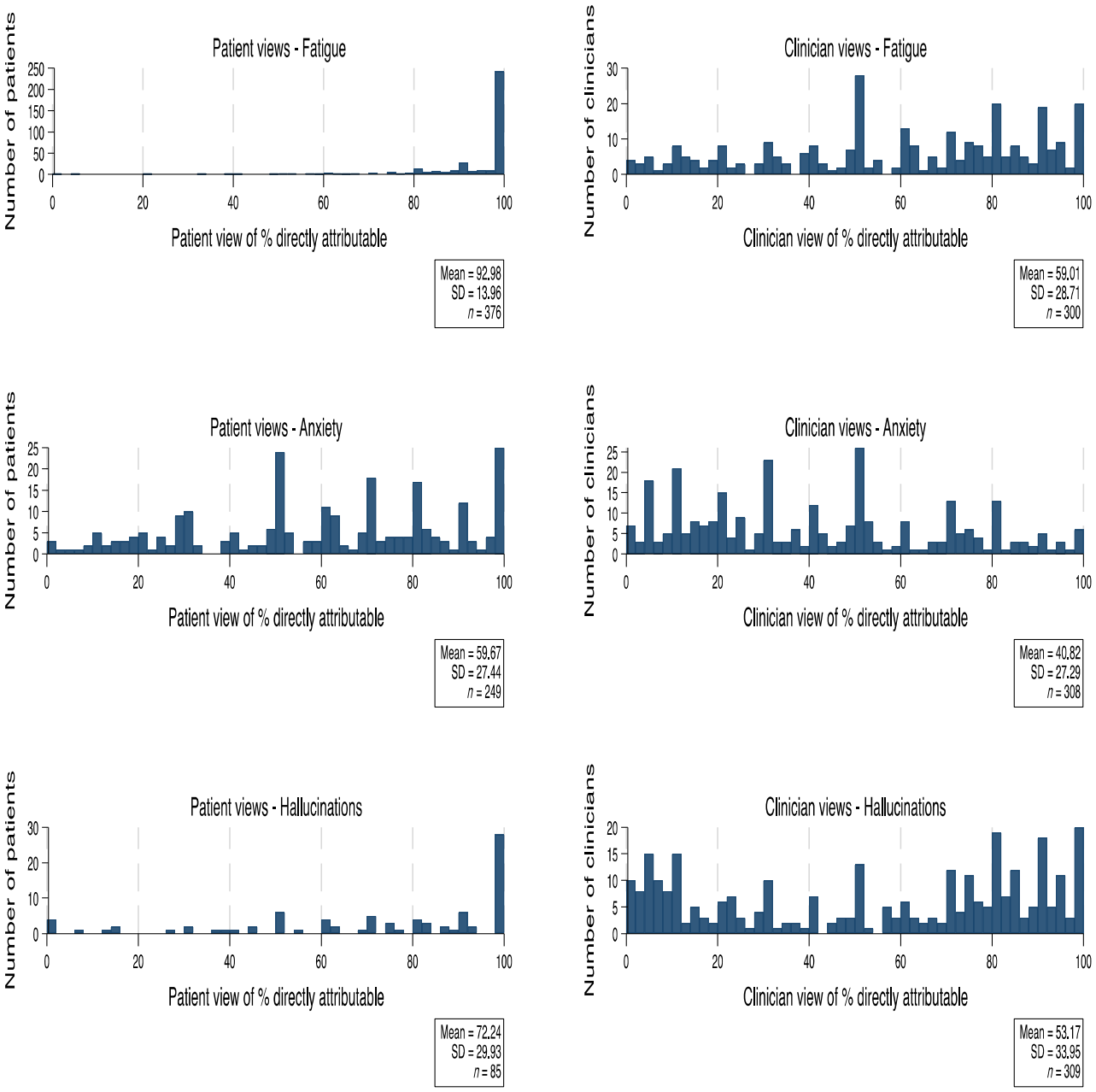


Figure 2. Histograms demonstrating patient and clinician views of the percentage of a given symptom considered to be attributable to the direct effects of SLE on the nervous system

'Only 10% of brain scans get reviewed by a neuro-radiologist … there have been very different results when they are reported on by neuro-radiologists … so a rheumatologist may say "oh this scan is normal" because that's what the report says, but 20–30% of those scans will not be normal.' (Ppt 119, neurologist, England)

Although the majority of clinicians specified that brain imaging is usually normal in NPSLE, 11% of clinicians surveyed stated that they would not diagnose NPSLE without abnormal brain imaging, and others discussed in interview that they would require some form of diagnostic test evidence:

'In order to diagnose CNS lupus or CNS vasculitis we would have to have evidence of CNS inflammation … You would need to have changes on their brain scans although not all will have, but there would have to be evidence in terms of cells in the spinal fluid, or they've got APS which has caused strokes.' (Ppt 66, neurologist, England)

This insistence on diagnostic test evidence was raised as a concern by other clinicians who reported that the majority of SLE NP symptoms relapse-remit with no identifiable structural changes or diagnostic testing evidence, but that does not exclude them from being directly attributable to the disease and therefore requiring immunosuppression:

'The disease is affecting your blood vessels, we often can't test this, but that is very systemic, the nerves in your blood vessels are everywhere, so why wouldn't that be an explanation for lots of these neurological symptoms these lupus

and other autoimmune patients get? There is this systemic diffuse presentation that is very hard when doctors think in that very limited box of neurology to localize.' (Ppt 58, neurologist, USA)

The rapidly evolving research in neuroinflammation and multiple potential aetiologies was felt to not be reaching some clinicians, or applied in clinical practice:

'My later training is that there is a definite link between other areas of inflammation and brain inflammation, so even depression and psychosis these are inflammatory illnesses. So we have to challenge what we were taught and some doctors will be lagging behind … It's not just the blood brain barrier, it's stuff to do with the vagus nerve, the autonomic, cytokines and the activated microglia in the brain.' (Ppt 52, psychiatrist, England)

Sub-theme: '*A significant level of bias*' can influence clinician decision making

Many clinicians acknowledged the influence of '*a significant level of bias*' (Ppt 59, neurologist, England) in assessments, particularly from having recently seen a patient with a specific NP symptom, or from having seen few patients with certain symptoms: '*In my particular case, I have never had a patient with lupus with hallucinations due to the disease but rather they were due to other causes* [like] *toxic-metabolic. This is why my response percentage is so low'*. (Ppt 64, rheumatologist, Europe). Clinicians reflected that they were more likely to identify and directly attribute symptoms that were observable, including extreme changes in behaviour: '*because the mania and delusions can be so outrightly evident*' (Ppt 54, rheumatologist, India), as opposed to more subtle changes or those requiring a patient to volunteer the information.

Gender, age and/or ethnicity were reported as sometimes influencing NPSLE (mis)diagnosis, particularly in relation to perceptions of over-attribution of physiological symptoms in females to psychological or somatoform causes. This included patient reports of their female gender being referred to when receiving a (mis)diagnosis: '*He said I see lots of women like you with nothing wrong*' (Ppt 47, England). This view was also reflected in clinician reports:

'It is common for women especially to be told that their symptoms are psychosomatic … as soon as emotion is displayed it all too commonly becomes the cause of everything else. This bias causes medical negligence.' (Ppt 217, GP, England)

Multiple clinicians made references to perceived ethnic differences in NP symptom frequency, and there was evidence from clinician and patient reports that the ethnicity of the patient may influence the likelihood of being (mis)diagnosed with NPSLE. This included a clinician's report of a Black male's diagnosis of NPSLE being delayed because the clinicians initially assumed his psychosis was due to 'cultural' cannabis use, and some White participants reporting being told that their ethnicity meant they would be unlikely to have organ involvement. Several participants also questioned whether the socio-demographic characteristics of the clinician influenced NPSLE attribution decisions. There was evidence of this in the quantitative data demonstrating that male clinicians had a higher frequency than female clinicians of perceiving that patients over-played physical symptoms ($P = 0.002$). In addition, female clinicians had higher mean estimations of symptoms being from the direct disease impact than male clinicians. For example, female clinicians estimated severe headaches as 52% directly attributable as opposed to male clinicians' mean estimation of 44% ($P = 0.018$).

Clinicians who divulged that they had experienced severe fatigue and cognitive dysfunction from long Covid or autoimmunity invariably felt that these symptoms were highly/wholly attributable to nervous system inflammation. There were suggestions that overall attitudes among clinicians towards these symptoms were now more orientated to a direct biological mechanism despite no laboratory evidence due to rapidly increasing knowledge and more clinicians having experienced the symptoms themselves from long Covid:

'I think there are all sorts of biological reasons for the fatigue that you wouldn't see on a scan or in tests … these doctors who say that fatigue is not biological or from the disease, have they never been unwell, so in terms of getting Covid or another illness, and experiencing it themselves?' (Ppt 84, psychiatrist, England)

Terminology differed between and within specialities and was found to influence diagnostic and attribution views. The term CNS lupus was sometimes used synonymously with CNS vasculitis, particularly by neurologists. Interviews revealed this implied a more limited range of NP symptoms as attributable than the more common term neuro-lupus or NPSLE, in line with patient experiences: '[rheumatologist] *said unless I had vasculitis in my brain, I didn't have CNS lupus*' (Ppt 827, Wales). The majority of other clinicians considered CNS vasculitis to be very rare and only one of many pathologies affecting the brains of SLE patients.

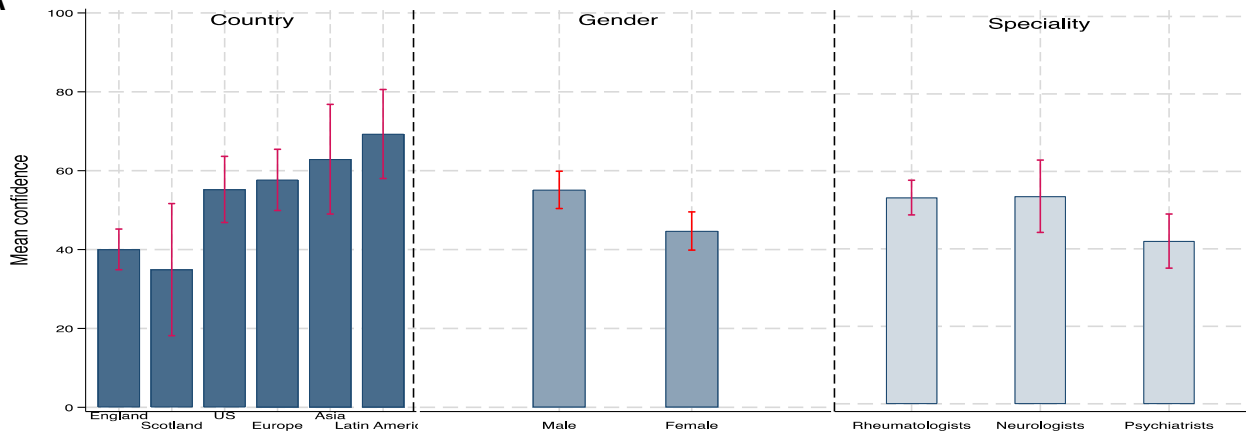
Theme 3: Consequences of misattributions and the contested role of co-diagnoses

Whilst most clinicians and almost all patients focused on problems of under-attribution and undertreatment, several neurologists warned of the dangers of overtreatment/wrong treatment if symptoms were over-attributed to direct SLE disease effects:

'It is essential to be able to discuss the possibility, indeed probability, that not all symptoms can be explained by structural damage/disease, as if one does not, one is consigning people to inadequate treatment and sometimes excessive treatment from a biological perspective.' (Ppt 152, neurologist, England)

Functional co-morbidities were reported by some clinicians to be more likely to occur in patients with chronic diseases as: '*the lupus could be a predisposing or acute precipitant*' (Ppt 312, neurologist, Mexico), and could co-exist, but require different treatment. This was a contentious topic with other clinicians suggesting that co-diagnoses were often inappropriate due to the disease itself directly causing these symptoms. Misdiagnoses were reported in both directions. Although some clinicians highlighted the importance of co-diagnoses being based on positive signs, common co-diagnoses such as fibromyalgia were perceived to have often been given due to absence of

A

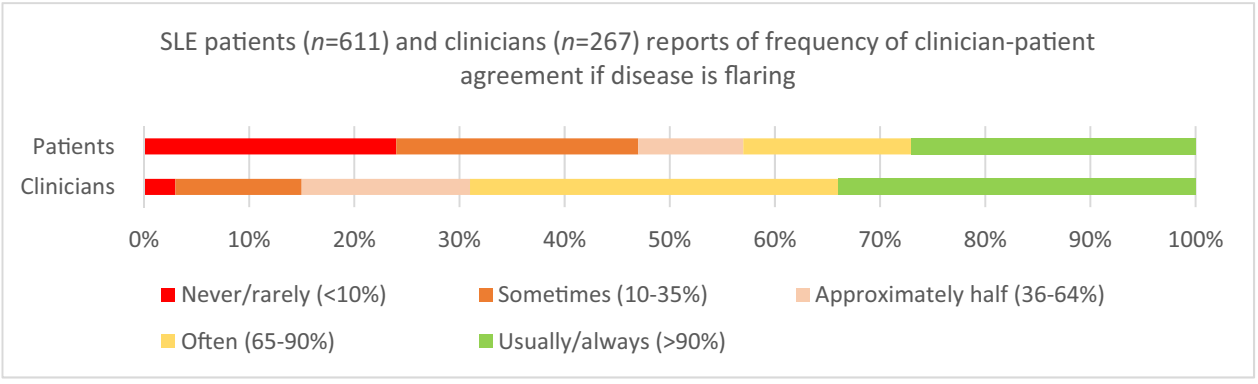


B

Category***	Mean (± SD) patient reports *n*=653 max	Mean (± SD) clinician reports *n*=368 max	Mean Difference	*p* Value (t test)
Level of patient-clinician agreement if flaring	3.02 (±1.91)	4.87 (±1.63)	1.85	<0.001
Asked if SLE is flaring	2.01 (±1.91)	4.27 (± 1.48)	2.26	<0.001

From 0=never to 6=always

C



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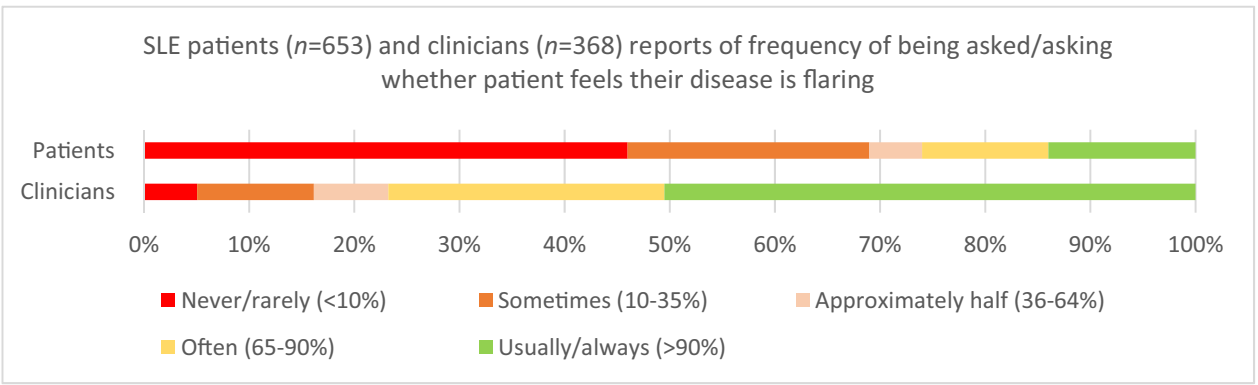
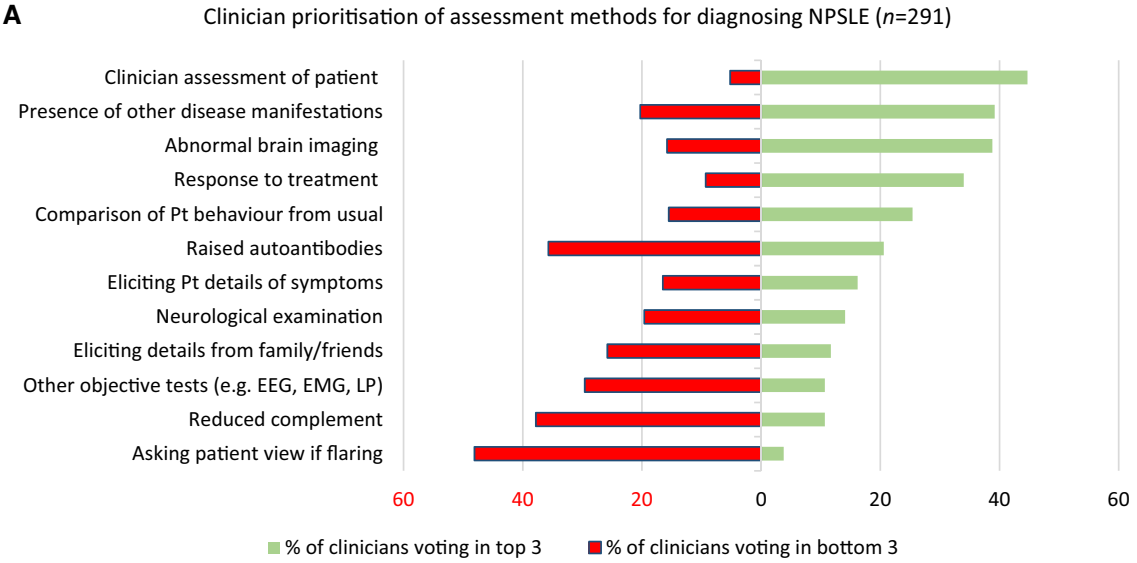


Figure 3. Clinician confidence, patient-clinician concordance, and frequency of eliciting patient views of disease activity. (**A**) Clinician confidence in diagnosing NPSLE. (**B**) Significant differences between patient and clinician views of flaring and eliciting patient views. From 0 (never) to 6 (always). (**C**) Clinician–patient concordance as to whether SLE is flaring. (**D**) Clinician and patient reports as to frequency of asking/being asked if SLE is flaring

A



B

Diagnostic evidence	Illustrative participant quote
Invasiveness of brain biopsies, and inter-clinician disagreement	*The biggest disadvantage compared with other organs affected by lupus is very rarely you biopsy a brain. So if you think they have lupus in the kidney, usually they would also have something like high blood pressure, then it's easy you do just a little punch of the kidney…can't just do a little punch biopsy of the brain…And it is not so easy because we all often also, we disagree on these diagnoses, it is so difficult because even between us we don't agree* (Ppt 24, rheumatologist, England)
Normal MRIs and reticence to do Lumbar punctures	*You can do an MRI but they're often normal, or a lumbar puncture but that's quite invasive and rheumatologists don't like to do that and it's certainly not without risk so I certainly wouldn't want to* (Ppt 228, rheumatologist, England)
Many autoantibodies are undiscovered	*There will be autoantibodies in encephalitis and lupus that we just haven't discovered yet…We can't say just because investigations are normal it's not there* (Ppt 59, neurologist, England)
More accurate complement testing only available in specialised laboratories	*Routine assays for C3 and C4 don't only measure native C3 and C4 but also the large activation fragments, C3b, C4b etcetera, so can give "normal" levels despite huge activation/consumption…* [Instead, clinicians should be] *measuring complement activation products – C3 fragments, C5a, terminal complement complex…Many specialist immunology labs already offer one or more of these* (Ppt 81, Immunologist, Wales)

Figure 4. Clinician rankings of diagnostic evidence, and limitations of existing tests.(**A**) Clinician results for top and bottom rankings for diagnostic evidence. (**B**) Limitations of current diagnostic tests and investigations. EEG: electroencephalogram; EMG: electromyography; LP: lumbar puncture

diagnostic or visible markers of SLE/NPSLE. This included during telephone consultations, and on occasions in writing when refusing a referral, when positive signs had not been assessed.

Clinicians and patients reported many cases where NPSLE symptoms not initially attributed to SLE, and therefore not correctly treated, had led to permanent damage. Clinicians highlighted the risk of cumulative, initially undetected or mis-attributed, PNS (usually small fibre and autonomic neuropathy) and CNS damage, particularly white matter changes and brain atrophy.

Theme 4: Patient reporting and attributional accuracy

Sub-theme: '*Patients are not good at assessing themselves in terms of symptoms*'

Clinicians perceived that patients both under and over-played their symptoms significantly more frequently than patients reported having done so ($P < 0.001$). A common viewpoint was that: '*Patients are not good at assessing themselves in terms of symptoms*' (Ppt 42, neuroimmunologist, England), partly as a result of the often long and convoluted path from 'root' causes to presenting symptoms:

'Often [patients] *don't understand the root cause, so fatigue can make tingling worse for example, therefore lack of sleep can be the root cause of sensory problems, so interpretation can be difficult and can be a long way from what the actual symptom presents.'* (Ppt 72, neurologist, England)

It was implied (and on occasions explicitly expressed) in some clinician interviews that if a patient's self-reports did not have corresponding laboratory or visible evidence then their reports were considered to be the inaccurate version of events:

'Some patients, for them it is not a lie, but I see the patient objectively and their symptoms I see do not match how bad the symptoms they're saying … from their blood test results or objective finding it doesn't say the same.' (Ppt 18, rheumatologist, Japan)

Adverse medical experiences, particularly early SLE symptoms being misattributed to psychological causes, had reduced some patients' confidence in their own, and their clinician's, ability to interpret their symptoms. In addition, attributional insight would be reduced in acute flares affecting insight or cognition, such as psychosis or acute confusion: '*I'll directly ask how's your memory been, and they'll say fine and then you'll see two pairs of glasses on their head or some indicator that their memory is not fine*' (Ppt 51, psychiatrist, England). Some clinicians hypothesized that some patients may self-attribute symptoms more highly to the direct disease effect to reduce the anticipated medical and societal (and sometimes self) stigma of having a primary or unrelated mental health condition. However, patients generally expected and accepted that some of their symptoms, particularly anxiety and depression, arose in part from the challenges of coping with a chronic disease.

Sub-theme: [Patients] *'are often expert diagnosticians in their own right'*

Almost all patients demonstrated that they had carefully considered various types of evidence when discussing attributional clues, such as the change in their NP symptoms on medication. Patient self-monitoring included manifestations that were absent from NPSLE guidelines, and rarely discussed with clinicians as related to SLE/NPSLE. This included a diverse range of symptoms such as increased nightmares, or difficult to articulate symptoms such as a 'feeling of unreality'. Patients regularly discussed in interviews that their initial self-assessments had often eventually been verified: '*9/10 times I've been right*' (several patients). Nurses and psychiatrists in particular referred to valuing patient attributional insights:

'*Patients often arrive in clinic having had multiple assessments, having researched their own condition to a very high level and having worked hard to understand what is going on with their own body. Even if I think they have got something wrong in their analysis, it behoves me to question my own assumptions and misconceptions as much as theirs … entails accepting they are often expert diagnosticians in their own right.*' (Ppt 158, psychiatrist, Wales)

Patient-reported frequency of being asked their opinion of whether they were flaring was significantly weakly to moderately positively correlated with measures of satisfaction with life and care. (For example, with trust in clinician, $r = 0.38$, $P < 0.001$.) Multiple participants (both clinician and patient) reported mutually trusting patient–clinician relationships and felt that the teamwork and continuity had aided the diagnostic process:

'My rheumatologist I am very close to, he showed lots of empathy … he knows and recollects every single symptom I have ever told him … he will say "oh yes 5 years ago you had this", and he tries to put it together and listens to us so well.' (Ppt 582, India)

Discussion

Clinicians openly acknowledged limitations in NPSLE knowledge and diagnostic tests, and demonstrated a wide range of estimates and opinions regarding the attribution of neuropsychiatric symptoms. Clinicians ranked their own assessments as the most important evidence in diagnosing NPSLE/NPSLE flares, over both diagnostic tests and patient reports/views. The conflicting views and high variance in attribution estimates adds to previously raised concerns that clinician judgement has limited accuracy when assessing purely subjective symptoms [5, 6]. Our data suggest that diagnosis of NPSLE may be influenced as much by clinician factors, such as views on attributability of NP symptoms in general, and patient (and possibly clinician) sociodemographic characteristics, as by the individual patient's symptoms. Major challenges for clinicians in accurately attributing subjective symptoms included, along with time constraints, rarely being in possession of the full picture due to patient reticence in reporting neuropsychiatric symptoms [5], and the limited availability and accuracy of diagnostic tests, which was also identified in previous studies [4, 17, 18].

Importantly, it was clear that the concept of attribution was not understood uniformly between clinicians and patients, or even within each group. Comprising notions of both causality and pathogenicity, to say that a neuropsychiatric symptom is directly attributable to SLE could potentially mean: (i) the symptoms are due to pathology directly evident in the brain/nervous system and associated with active SLE disease (for example, weakness in the limbs with clear evidence of inflammation in the spinal cord); or (ii) the symptoms are clearly associated with active SLE (for example, cognitive dysfunction or headaches) but without a discrete neurological pathology that is detectable with existing testing. Although in both cases the symptoms may benefit from immunotherapy, we identified that some clinicians, particularly neurologists, were less inclined to consider (ii) directly attributable, suggesting possible widespread under-attribution and under-treatment of these often life-changing diffuse symptoms.

Our clinician participants reported that brain imaging was often normal in NPSLE, and serology was more likely to be normal than in SLE involving other organs. This is in accordance with a study finding that patients without anti-dsDNA antibodies at SLE diagnosis were more at risk for developing NPSLE [8], although patients with concurrent APS are thought to have a higher risk of developing NPSLE [19, 20]. In addition to many patients potentially having as yet untested/undiscovered biomarkers, autoantibodies may be

negative for many additional reasons including long-standing disease, immunosuppression and co-morbid immunodeficiency [21]. Moreover, knowledge of potential biomarkers such as novel autoantibodies, cytokines, chemokines [22] and neuronal damage markers is rapidly evolving, and not yet reflected in clinical practice or guidelines, including the ACR NPSLE criteria [23] relied upon by many clinicians. There is an urgent requirement for funding and research to improve NPSLE diagnostic tests, including brain imaging and identifying further blood and CSF biomarkers across a range of inflammatory/immunological and neuronal damage markers. However, given the heterogeneity of NPSLE, it may be appropriate to expect that biomarkers will be found for specific neurological or neuropsychiatric phenotypes, rather than for NPSLE *per se*. For example, although rare, aquaporin 4 (AQP4) and anti-myelin oligodendrocyte glycoprotein (MOG) antibodies are helpful in attributing neurological symptoms to direct antibody pathogenic mechanisms in some rare cases of lupus optic neuropathy and lupus myelopathy [24].

Despite these identified limitations in knowledge, guidelines and diagnostic tests, and there being many things that 'only a patient knows' [25] in relation to assessing changes in the diffuse neuropsychiatric symptoms most common in NPSLE [12], patient reports and self-interpretations were the lowest priority for clinicians in diagnosing NPSLE. The undervaluing of subjectivity was evident in the reports of non-externally verifiable symptoms being more often misattributed, 46% of patients reporting they had never/rarely been asked if they considered their SLE was flaring, and the clinician and patient desire for positive diagnostic tests to verify subjective reports. It is also reflected in research where qualitative data is often considered inferior [26], yet high-quality qualitative research, such as that by Eudy *et al.* differentiating types of SLE [27], is essential for generating deeper understanding and novel insights [28]. Our findings add weight to Blease and Bell's suggestion that patients 'may be the most underutilized resource for mitigating diagnostic error' [29], and to calls for improved 'bidirectional trust' [29], and diagnostic partnerships between patients and clinicians [30]. We identified that collaborative and empowering medical relationships likely facilitated more informed attributional decisions by combining patients' depth of experiential knowledge with clinicians' breadth of medical knowledge [31]. Further development of NPSLE attribution guidelines, such as those by Bortoluzzi *et al.* [1], could therefore consider the multiple benefits (including diagnostic and patient satisfaction) of incorporating eliciting the patient views on their symptoms' attribution as one of the areas of evidence.

The importance of combining diagnostic tests, clinician assessments and patient reports/views to ensure more accurate attributional decisions is evidenced in studies of other conditions. These include findings of: poor correlation between various objective and subjective measures [32–34], and clinicians' assessments lacking consistency [35], accuracy and reproducibility [36], and differing from patients self-assessments [37], as our study also demonstrated. Although there has been great progress made in valuing patient views in some research [27, 38–40], some of the medical literature remains explicitly biased against the accuracy of patients' self-assessments, and the legitimacy of experiential knowledge is often questioned [41]. For example, a study of cognitive impairment in MS patients labelled patients whose subjective self-assessment was discordant with the concurrent objective measurement as 'overestimators' or 'underestimators' [42]. Consistent with the expressed views of some clinicians in our study, the subjective values were assumed to be incorrect, although the discordance is likely to be related to the challenges of measuring a complex and non-unitary construct such as 'cognition', only facets of which are captured by any one test.

Patients in our study demonstrated a high level of knowledge about their conditions, 'attributional insight' [43] and reasoning comparable to that used by clinician participants in assessments, such as evaluating how symptoms responded to medication. This included self-monitoring manifestations not recognized by many clinicians or included in any current guidelines, such as increasing nightmares that D'Cruz theorizes precedes an NPSLE flare in some patients [44]. Interestingly, those clinicians who had gained experiential knowledge themselves (including, for example, from long Covid), and traversed the usual barrier to understanding between patients with 'lived' knowledge and clinicians with 'learnt' knowledge, leant strongly towards a biological explanation for many NP symptoms. However, it is also important to consider the psychosocial impact of life-changing diseases, the effect of medications such as corticosteroids, infections and co-morbidities, and avoid over/mis-attributing [18] symptoms to the direct autoimmune disease activity, and thus over/mis-treating symptoms. For example, in the case of non-epileptic seizures [9], treatment with immunosuppression or anti-epileptics can be harmful and ineffective.

The limitations in NPSLE knowledge and tests appeared to increase the propensity for, and adverse influence of, clinician cognitive bias. This incorporated acknowledgements of recency, referral and experience biases, and suggestions of confirmation bias occurring when clinicians attributed new SLE symptoms to previous mental health mis/diagnoses. Potential gender and ethnic biases were discussed, particularly the possible over-attribution of physiological symptoms in females to psychological or somatoform aetiologies. An additional finding is that consistency in terminology between specialities should be encouraged as it was found to influence the range of symptoms individual clinicians were considering in assessments, particularly 'CNS lupus' encompassing a narrower range of symptoms than NPSLE. This often excluded the majority of diffuse NP symptoms more common in SLE [12], that have no identifiable structural changes (at least initially), yet may be directly attributable to the disease and thus benefit from immunosuppression. CNS lupus also by definition excludes the peripheral nervous system (PNS). The PNS is increasingly recognized in research, but not yet widely in clinical practice, as being directly affected in many patients with systemic autoimmune rheumatic diseases, particularly small fibre neuropathy (SFN) [45], and autonomic dysfunction [46, 47]. Therefore, NPSLE seems to be the most appropriate term due to it incorporating neurological, psychiatric, diffuse, focal, CNS and PNS symptoms.

Although we are endorsing valuing patient views and input, patient self-assessments have their own limitations and inaccuracies. Several studies have found differences in reporting by sociodemographic group, such as more underplaying of symptom severity in the elderly [48]. Numerous studies report that concurrent depression may lead to perceptions of higher symptom burden [34, 49]. Patients with the most severe NPSLE affecting insight and/or cognition may lose attributional insight, and the more recently diagnosed will need time

and support to develop the attributional insight demonstrated by more experienced patients. Limitations of the INSPIRE project overall can be found in our first INSPIRE paper [5] and Supplementary Data S1 (available at *Rheumatology* online), and include the self-selecting nature of online recruitment, recall bias [50], and no means to verify the accuracy of either patient or clinician interpretations. Symptoms were selected for study inclusion due to one of their aetiologies being neuropsychiatric in SLE patients, but some (for example, difficulty swallowing or bladder symptoms) have multiple potential aetiologies that add to the complexity of attribution. There is also no consensus in the literature of an accepted term that encompasses all the neuropsychiatric experiences of these patients. After extensive consultation with patients and clinicians, the term 'symptom' was selected as this was the most familiar and widely understood. We will continue to use this term throughout the INSPIRE studies in order to ensure consistency and conceptual coherence between the survey and interview terminology and the analyses. This has a limitation in that some 'symptoms' may be classified in other research and care as 'syndromes', 'manifestations' or 'events', and terminology may have different connotations between and within specialities, and between patients and clinicians.

Additional limitations of this study included that clinicians may value patient views more than the data suggests due to some diagnostic evidence items not all being clearly mutually exclusive. For example, the item 'Clinician assessment of patient presentation' could incorporate eliciting patient symptoms. In addition, some clinicians specified that they valued all items of diagnostic evidence, and therefore there may not have been much difference in value given to those ranked in the top and bottom three by some clinicians. However, the additional data demonstrating limited trust in accuracy of patient symptom reporting, and the clearly articulated desire for diagnostic test evidence adds to the validity of the rankings of prioritization data. Strengths include the multidisciplinary team approach and patients being equally valued members of the INSPIRE team. The use of participant validation [16], whereby we discussed initial findings with multiple participants (clinicians and patients) to ensure we had fairly and accurately represented the range of experiences and viewpoints, adds to the confidence in the reliability of our data [16].

Conclusion

In conclusion, we found high variability and often contrasting views regarding attribution and the use of diagnostic methods for NPSLE. Diagnostic tools are currently inadequate and rarely detect diffuse neuropsychiatric symptoms (such as cognitive dysfunction and headache) that can be directly attributable and therefore benefit from immunosuppression. The identified inter-clinician inconsistency in terminology and varied interpretations of 'direct attributability' suggests greater discussion and homogenization between specialities is required. Our qualitative findings suggest multiple potential benefits (including diagnostic and patient satisfaction) of greater incorporation of patients' attributional insights and experiential knowledge into diagnostic decisions and attribution guidelines. This hypothesis will be tested quantitatively in our future INSPIRE studies.

Supplementary material

Supplementary material is available at *Rheumatology* online.

Data availability

Anonymized data will be available on reasonable request following the completion of the INSPIRE studies.

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Biologics may be **less effective** in patients who are **overweight**[1,2]

Eligible patients, weighing ≥90kg with PsA and concomitant moderate to severe PsO, may need an individualised treatment approach[4,5]

>6 in 10 adults over the age of 18 years in England are estimated to be overweight or living with obesity[3]

Click here to visit our HCP portal and learn more

Cosentyx® (secukinumab) provides **flexible dosing** based on your eligible patients' needs*[4,5]

Loading dose

Week **0**	Week **1**	Week **2**	Week **3**	Week **4**
300 mg	300 mg	300 mg	300 mg	300 mg

Maintenance dosing

Body weight **<90 kg**: 300 mg Monthly

Based on clinical response, consider up-titration
≥90 kg patients not responding to monthly maintenance dosing: 300 mg every **2 weeks**

Adapted from Cosentyx® (secukinumab) SmPC.[4,5]

*For adult patients with PsA and concomitant moderate to severe PsO, the recommended dose of Cosentyx is 300 mg with initial dosing at Weeks 0, 1, 2, 3 and 4, followed by **monthly maintenance dosing**. Based on clinical response, a maintenance dose of 300 mg **Q2W** may provide additional benefit for patients with a body weight of **90 kg or higher**.[4,5]

Cosentyx is indicated for the treatment of moderate to severe plaque psoriasis in adults, children and adolescents from the age of 6 years who are candidates for systemic therapy; active psoriatic arthritis in adult patients (alone or in combination with methotrexate) when the response to previous disease-modifying anti-rheumatic drug therapy has been inadequate; active ankylosing spondylitis in adults who have responded inadequately to conventional therapy; active non-radiographic axial spondyloarthritis with objective signs of inflammation as indicated by elevated C-reactive protein and/or magnetic resonance imaging evidence in adults who have responded inadequately to non-steroidal anti-inflammatory drugs; active moderate to severe hidradenitis suppurativa (acne inversa) in adults with an inadequate response to conventional systemic therapy; active enthesitis-related arthritis in patients 6 years and older (alone or in combination with methotrexate) whose disease has responded inadequately to, or who cannot tolerate, conventional therapy; active juvenile psoriatic arthritis in patients 6 years and older (alone or in combination with methotrexate) whose disease has responded inadequately to, or who cannot tolerate, conventional therapy.[4,5]

PsA, psoriatic arthritis; PsO, plaque psoriasis; Q2W, every 2 weeks.

References: 1. Warren RB, et al. *J Invest Dermatol* 2015;135:2632–2640; **2.** Warren RB, et al. *Br J Dermatol* 2019;180(5):1069–1076; **3.** Office for Health Improvement and Disparities. Obesity profile: short statistical commentary May 2024. Available at: https://www.gov.uk/government/statistics/update-to-the-obesity-profile-on-fingertips/obesity-profile-short-statistical-commentary-may-2024 [Accessed August 2024]; **4.** Cosentyx® (secukinumab) GB Summary of Product Characteristics; **5.** Cosentyx® (secukinumab) NI Summary of Product Characteristics.

NOVARTIS

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Cosentyx® (secukinumab) Great Britain Prescribing Information.

Please refer to the Summary of Product Characteristics (SmPC) before prescribing.

Indications: Treatment of: moderate to severe plaque psoriasis in adults, children and adolescents from the age of 6 years who are candidates for systemic therapy; active psoriatic arthritis in adults (alone or in combination with methotrexate) who have responded inadequately to disease-modifying anti-rheumatic drug therapy; active ankylosing spondylitis in adults who have responded inadequately to conventional therapy; active non-radiographic axial spondyloarthritis (nr-axSpA) with objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI) evidence in adults who have responded inadequately to non-steroidal anti-inflammatory drugs; active enthesitis-related arthritis and juvenile psoriatic arthritis in patients 6 years and older (alone or in combination with methotrexate) whose disease has responded inadequately to, or who cannot tolerate, conventional therapy; active moderate to severe hidradenitis suppurativa (acne inversa) in adults with an inadequate response to conventional systemic HS therapy. **Presentations:** Cosentyx 75 mg solution for injection in pre-filled syringe; Cosentyx 150 mg solution for injection in pre-filled syringe; Cosentyx 150 mg solution for injection in pre-filled pen; Cosentyx 300 mg solution for injection in pre-filled pen. **Dosage & Administration:** Administered by subcutaneous injection at weeks 0, 1, 2, 3 and 4, followed by monthly maintenance dosing. Consider discontinuation if no response after 16 weeks of treatment. Each 75 mg dose is given as one injection of 75 mg. Each 150 mg dose is given as one injection of 150 mg. Each 300 mg dose is given as two injections of 150 mg or one injection of 300 mg. If possible avoid areas of the skin showing psoriasis. *Plaque Psoriasis:* Adult recommended dose is 300 mg. Based on clinical response, a maintenance dose of 300 mg every 2 weeks may provide additional benefit for patients with a body weight of 90 kg or higher. Adolescents and children from the age of 6 years: if weight ≥ 50 kg, recommended dose is 150 mg (may be increased to 300 mg as some patients may derive additional benefit from the higher dose). If weight < 50 kg, recommended dose is 75 mg. *Psoriatic Arthritis:* For patients with concomitant moderate to severe plaque psoriasis see adult plaque psoriasis recommendation. For patients who are anti-TNFα inadequate responders, the recommended dose is 300 mg, 150 mg in other patients. Can be increased to 300 mg based on clinical response. *Ankylosing Spondylitis:* Recommended dose 150 mg. Can be increased to 300 mg based on clinical response. *nr-axSpA:* Recommended dose 150 mg. *Enthesitis-related arthritis and juvenile psoriatic arthritis:* From the age of 6 years, if weight ≥ 50 kg, recommended dose is 150 mg. If weight < 50 kg, recommended dose is 75 mg. *Hidradenitis suppurativa:* Recommended dose is 300 mg monthly. Based on clinical response, the maintenance dose can be increased to 300 mg every 2 weeks. **Contraindications:** Hypersensitivity to the active substance or excipients. Clinically important, active infection. **Warnings & Precautions:** *Infections:* Potential to increase risk of infections; serious infections have been observed. Caution in patients with chronic infection or history of recurrent infection. Advise patients to seek medical advice if signs/symptoms of infection occur. Monitor patients with serious infection closely and do not administer Cosentyx until the infection resolves. Non-serious mucocutaneous candida infections were more frequently reported for secukinumab in the psoriasis clinical studies. Should not be given to patients with active tuberculosis (TB). Consider anti-tuberculosis therapy before starting Cosentyx in patients with latent TB. *Inflammatory bowel disease (including Crohn's disease and ulcerative colitis):* New cases or exacerbations of inflammatory bowel disease have been reported with secukinumab. Secukinumab, is not recommended in patients with inflammatory bowel disease. If a patient develops signs and symptoms of inflammatory bowel disease or experiences an exacerbation of pre-existing inflammatory bowel disease, secukinumab should be discontinued and appropriate medical management should be initiated. *Hypersensitivity reactions:* Rare cases of anaphylactic reactions have been observed. If an anaphylactic or serious allergic reactions occur, discontinue immediately and initiate appropriate therapy. *Vaccinations:* Do not give live vaccines concurrently with Cosentyx; inactivated or non-live vaccinations may be given. Paediatric patients should receive all age appropriate immunisations before treatment with Cosentyx. *Latex-Sensitive Individuals:* The removable needle cap of the 75mg and 150 mg pre-filled syringe and 150mg pre-filled pen contains a derivative of natural rubber latex. *Concomitant immunosuppressive therapy:* Combination with immunosuppressants, including biologics, or phototherapy has not been evaluated in psoriasis studies. Cosentyx was given concomitantly with methotrexate, sulfasalazine and/or corticosteroids in arthritis studies. Caution when considering concomitant use of other immunosuppressants. **Interactions:** Live vaccines should not be given concurrently with secukinumab. No interaction between Cosentyx and midazolam (CYP3A4 substrate) seen in adult psoriasis study. No interaction between Cosentyx and methotrexate and/or corticosteroids seen in arthritis studies. **Fertility, pregnancy and lactation:** *Women of childbearing potential:* Use an effective method of contraception during and for at least 20 weeks after treatment. *Pregnancy:* Preferably avoid use of Cosentyx in pregnancy. *Breast feeding:* It is not known if secukinumab is excreted in human breast milk. A clinical decision should be made on continuation of breast feeding during Cosentyx treatment (and up to 20 weeks after discontinuation) based on benefit of breast feeding to the child and benefit of Cosentyx therapy to the woman. *Fertility:* Effect on human fertility not evaluated. **Adverse Reactions**: *Very Common (≥1/10):* Upper respiratory tract infection. *Common (≥1/100 to <1/10):* Oral herpes, headache, rhinorrhoea, diarrhoea, nausea, fatigue. *Uncommon (≥1/1,000 to <1/100):* Oral candidiasis, lower respiratory tract infections, neutropenia, inflammatory bowel disease. *Rare (≥1/10,000 to <1/1,000)*: anaphylactic reactions, exfoliative dermatitis (psoriasis patients), hypersensitivity vasculitis. *Not known:* Mucosal and cutaneous candidiasis (including oesophageal candidiasis). *Infections:* Most infections were non-serious and mild to moderate upper respiratory tract infections, e.g. nasopharyngitis, and did not necessitate treatment discontinuation. There was an increase in mucosal and cutaneous (including oesophageal) candidiasis, but cases were mild or moderate in severity, non-serious, responsive to standard treatment and did not necessitate treatment discontinuation. Serious infections occurred in a small proportion of patients (0.015 serious infections reported per patient year of follow up). *Neutropenia:* Neutropenia was more frequent with secukinumab than placebo, but most cases were mild, transient and reversible. Rare cases of neutropenia CTCAE Grade 4 were reported. *Hypersensitivity reactions:* Urticaria and rare cases of anaphylactic reactions were seen. *Immunogenicity:* Less than 1% of patients treated with Cosentyx developed antibodies to secukinumab up to 52 weeks of treatment. *Other Adverse Effects:* The list of adverse events is not exhaustive, please consult the SmPC for a detailed listing of all adverse events before prescribing. **Legal Category:** POM. **MA Number & List Price:** PLGB 00101/1205 – 75 mg pre-filled syringe x 1 - £304.70; PLGB 00101/1029 - 150 mg pre-filled pen x2 £1,218.78; PLGB 00101/1030 - 150 mg pre-filled syringe x2 £1,218.78; PLGB 00101/1198 – 300 mg pre-filled pen x 1 £1218.78. **PI Last Revised:** June 2023. Full prescribing information, (SmPC) is available from: Novartis Pharmaceuticals UK Limited, 2nd Floor, The WestWorks Building, White City Place, 195 Wood Lane, London, W12 7FQ. Telephone: (01276) 692255.

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Adverse Event Reporting:

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard. Adverse events should also be reported to Novartis via uk.patientsafety@novartis.com or online through the pharmacovigilance intake (PVI) tool at www.novartis.com/report.

If you have a question about the product, please contact Medical Information on 01276 698370 or by email at medinfo.uk@novartis.com

Cosentyx® (secukinumab) Northern Ireland Prescribing Information.

Please refer to the Summary of Product Characteristics (SmPC) before prescribing.

Indications: Treatment of: moderate to severe plaque psoriasis in adults, children and adolescents from the age of 6 years who are candidates for systemic therapy; active psoriatic arthritis in adults (alone or in combination with methotrexate) who have responded inadequately to disease-modifying anti-rheumatic drug therapy; active ankylosing spondylitis in adults who have responded inadequately to conventional therapy; active non-radiographic axial spondyloarthritis (nr-axSpA) with objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI) evidence in adults who have responded inadequately to non-steroidal anti-inflammatory drugs; active enthesitis-related arthritis and juvenile psoriatic arthritis in patients 6 years and older (alone or in combination with methotrexate) whose disease has responded inadequately to, or who cannot tolerate, conventional therapy; active moderate to severe hidradenitis suppurativa (acne inversa) in adults with an inadequate response to conventional systemic HS therapy. **Presentations:** Cosentyx 150 mg solution for injection in pre-filled pen; Cosentyx 300 mg solution for injection in pre-filled pen. **Dosage & Administration:** Administered by subcutaneous injection at weeks 0, 1, 2, 3 and 4, followed by monthly maintenance dosing. Consider discontinuation if no response after 16 weeks of treatment. Each 150 mg dose is given as one injection of 150 mg. Each 300 mg dose is given as two injections of 150 mg or one injection of 300 mg. If possible avoid areas of the skin showing psoriasis. *Plaque Psoriasis:* Adult recommended dose is 300 mg monthly. Based on clinical response, a maintenance dose of 300 mg every 2 weeks may provide additional benefit for patients with a body weight of 90 kg or higher. Adolescents and children from the age of 6 years: if weight ≥ 50 kg, recommended dose is 150 mg (may be increased to 300 mg as some patients may derive additional benefit from the higher dose). If weight < 50 kg, recommended dose is 75 mg. However, 150mg solution for injection in pre-filled pen is not indicated for administration of this dose and no suitable alternative formulation is available. *Psoriatic Arthritis:* For patients with concomitant moderate to severe plaque psoriasis see adult plaque psoriasis recommendation. For patients who are anti-TNFα inadequate responders, the recommended dose is 300 mg, 150 mg in other patients. Can be increased to 300 mg based on clinical response. *Ankylosing Spondylitis:* Recommended dose 150 mg. Can be increased to 300 mg based on clinical response. *nr-axSpA:* Recommended dose 150 mg. *Enthesitis-related arthritis and juvenile psoriatic arthritis:* From the age of 6 years, if weight ≥ 50 kg, recommended dose is 150 mg. If weight < 50 kg, recommended dose is 75 mg. However, 150mg solution for injection in pre-filled pen is not indicated for administration of this dose and no suitable alternative formulation is available. *Hidradenitis suppurativa:* Recommended dose is 300 mg monthly. Based on clinical response, the maintenance dose can be increased to 300 mg every 2 weeks. **Contraindications:** Hypersensitivity to the active substance or excipients. Clinically important, active infection. **Warnings & Precautions:** *Infections:* Potential to increase risk of infections; serious infections have been observed. Caution in patients with chronic infection or history of recurrent infection. Advise patients to seek medical advice if signs/symptoms of infection occur. Monitor patients with serious infection closely and do not administer Cosentyx until the infection resolves. Non-serious mucocutaneous candida infections were more frequently reported for secukinumab than placebo in the psoriasis clinical studies. Should not be given to patients with active tuberculosis (TB). Consider anti-tuberculosis therapy before starting Cosentyx in patients with latent TB. *Inflammatory bowel disease (including Crohn's disease and ulcerative colitis):* New cases or exacerbations of inflammatory bowel disease have been reported with secukinumab. Secukinumab, is not recommended in patients with inflammatory bowel disease. If a patient develops signs and symptoms of inflammatory bowel disease or experiences an exacerbation of pre-existing inflammatory bowel disease, secukinumab should be discontinued and appropriate medical management should be initiated. *Hypersensitivity reactions:* Rare cases of anaphylactic reactions have been observed. If an anaphylactic or serious allergic reactions occur, discontinue immediately and initiate appropriate therapy. *Vaccinations:* Do not give live vaccines concurrently with Cosentyx; inactivated or non-live vaccinations may be given. Paediatric patients should receive all age appropriate immunisations before treatment with Cosentyx. *Latex-Sensitive Individuals:* The removable needle cap of the 150mg pre-filled pen contains a derivative of natural rubber latex. *Concomitant immunosuppressive therapy:* Combination with immunosuppressants, including biologics, or phototherapy has not been evaluated in psoriasis studies. Cosentyx was given concomitantly with methotrexate, sulfasalazine and/or corticosteroids in arthritis studies. Caution when considering concomitant use of other immunosuppressants. **Interactions:** Live vaccines should not be given concurrently with secukinumab. No interaction between Cosentyx and midazolam (CYP3A4 substrate) seen in adult psoriasis study. 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Adverse Event Reporting:

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard. Adverse events should also be reported to Novartis via uk.patientsafety@novartis.com or online through the pharmacovigilance intake (PVI) tool at www.novartis.com/report

If you have a question about the product, please contact Medical Information on 01276 698370 or by email at medinfo.uk@novartis.com