Barriers to therapy adherence in a group of Italian patients with systemic lupus erythematosus

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Abstract

Objective

The aim of this cross-sectional study was to investigate the prevalence and associated barriers of non-adherence to therapy (NAT) in a large cohort of Italian patients with systemic lupus erythematosus (SLE).

Methods

This multicentre cross-sectional study included 432 adult SLE patients. Adherence to therapy (AT) was assessed through the Medication Adherence Self-Report Inventory (MASRI) and adherence rates <80% were considered non-adherent. Psychological distress was evaluated via the Hospital Anxiety and Depression Scale (HADS). Barriers to AT were identified using a 32-item questionnaire addressing patient-, therapy-, socioeconomic-, and healthcare-related factors. Statistical analyses were performed to identify associations with NAT.

Results

NAT was observed in 38% of patients and was significantly associated with younger age ($p<0.001$) and higher HADS scores ($p<0.001$). Common patient-related barriers included forgetfulness (OR=11.56, $p<0.001$), daily routine changes (OR=5.29, $p<0.001$), and perceived hassle (OR=4.85, $p<0.001$). Key therapy-related barriers included fear (OR=29.15, $p<0.001$) and suffering (OR=5.73, $p<0.001$) side effects. Among socioeconomic barriers, only cost concerns were associated with NAT (OR=3.75, $p=0.002$). Healthcare system-related issues such as long waiting list (OR=2.01, $p=0.003$), divergent medical opinions (OR=2.10, $p=0.001$), and prescribed delay (OR=2.36, $p=0.004$) were more frequent in NAT patients. ROC curve analysis revealed an association between age ≤48 years and the presence of NAT and related behavioural barriers.

Conclusion

NAT is prevalent among Italian SLE patients and is driven by a combination of modifiable patient, therapy, and healthcare system barriers. Younger patients are at high risk of NAT due to behavioural and psychosocial barriers. Age-targeted interventions are needed to enhance adherence and outcomes.

Key words

therapy adherence, barriers, systemic lupus erythematosus

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Introduction

Systemic lupus erythematosus (SLE) is a highly complex chronic autoimmune disease of unknown aetiology (1). The term 'chronic disease' refers to a long-term condition (lasting at least six months), often multifactorial, that generally progresses slowly and requires continual treatment.

SLE can damage and impair multiple organs and tissues and affects both women and men but, with a female-to-male ratio of 9:1. The symptoms and severity of clinical manifestations are highly heterogeneous (2, 3). Unfortunately, to date, no definitive cure for SLE exists. However, various treatments are effective in controlling symptoms, slowing disease progression, and preventing long-term deterioration. These treatments include corticosteroids, antimalarial, immunosuppressive drugs, and biologic agents (2-4). Therapeutic success in chronic diseases, including SLE, also depends on optimal patient adherence to therapy (AT).

The World Health Organization (WHO) defines AT as the extent to which a person's behaviour aligns with the agreed recommendations by their physician regarding medication intake, dietary changes, and/or lifestyle modifications (2-4). While AT implies an active role of the patient, resulting from a bilateral agreement between physician and patient, 'compliance' is a quantitative measure of AT, indicating, for instance, the percentage of medication taken compared to the doses prescribed by the physician.

AT in patients with chronic diseases is generally low, due to the prolonged nature of the treatment and, need to take multiple medications, individual responses to specific drugs, and adverse effects caused by the medications themselves.

WHO estimates that the AT mean rate in chronic treatments is around 50% in developed countries. In patients with SLE, the rate of non-adherence to therapy (NAT) ranges from 3% to 75%, according to international literature (2, 3). Additionally, studies indicate that NAT in SLE contributes significantly to worsening clinical conditions, as it increases the risks of disease flares, progression, hospitalisations, morbidity, and mortality (3, 5-8).

Proper and consistent AT is thus, considered a key factor in controlling disease progression, improving patient conditions, and allowing a nearly normal life expectancy (3). The main domains influencing AT are related to: 1. the patients (patient's behaviour; 2. disease (disease course); 3. therapy; 4. socioeconomic aspects; 5. healthcare setting. For each of these domains, specific barriers can be identified that affect AT (1-3). According to international studies, the main barriers to AT in SLE patients include: concerns about potential side effects (therapy-domain), personal and socioeconomic reasons (socioeconomic domain), poor communication with healthcare providers (healthcare setting), forgetfulness and daily life commitments, and the erroneous belief that therapy does not significantly influence disease progression, the last two belonging to patient domain (9). Inasmuch as data on AT are lacking in the Italian population, and to improve management of SLE patients more effectively, we developed a self-administered questionnaire to define practical and perceived barriers to AT in an Italian cohort of 432 SLE patients.

Patients and methods

Patients

In this cross-sectional study, 432 adult patients fulfilling the 2019 EULAR/ACR criteria for SLE (10) were recruited from 2023 to 2025 at the Rheumatology Units of the Universities of Bari, Rome, Naples, and L'Aquila, with the collaboration of the SLE Italian Group-ODV.

The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Ethical Committee of the University of Bari Medical School (n.738/C.E., 13/12/20239). Informed consent was obtained from all subjects included in the study.

All participants were systematically interviewed using a standardised anonymous self-administered questionnaire (see the online Supplementary file). The questionnaire consisted of 5 different domains each including a set of barriers namely: 1. General (3-items);

2. Patient- (6-items); 3. Therapy-(6-items); 4. Socio-economic-related (6-items); and 5. Health care system-related barriers (11 items).

Assessment of AT

AT was assessed using part A of the well established Medication Adherence Self-report Inventory (MASRI) , which has also been validated in SLE (11), consisting of a 6-items questionnaire assessing the frequency of medication intake and , the estimated of the proportion of total amount of medication actually taken during the last month on a visual analogue scale (0 to 100%). Patients with a MASRI score<80% were defined as NAT, while patients with a MASRI ≥80% score were defined as AT.

In addition, AT was also assessed using the 8-item Morisky Medication Adherence Scale (MMAS-8) (12) and the 11-item General Medication Adherence Scale (GMAS) scale (13), both investigating barriers affecting AT.

Anxiety and depression assessment

Anxiety and depression were assessed using the Hospital Anxiety and Depression Scale (HADS), which consists of 7 items for anxiety and 7 items for depression (14). Each item is rated on a scale ranging from 0 (absence) to 3 (extreme presence). A score ≥8 indicates the presence of anxiety or depression.

Statistical analyses

Statistical analyses were performed using SPSS software (v. 21 for Windows). All data obtained were dichotomised. The Mann-Whitney U-test was used to compare differences between the two groups for continuous non-parametric variables. Chi-square and Fisher's exact tests were used to assess associations between categorical variables.

Variables with statistically significant associations at Fisher's exact test were analysed by multivariable logistic regression to adjust for gender and age as confounding variables. Receiver operating characteristics (ROC) analysis was used to define cut-off values that best discriminated the two groups. For all tests, statistical significance was set at *p*-value <0.05.

Table I. Patient characteristics and statistical comparison between patients adherent to therapy (AT) *vs*. those non-adherent (NAT).

Variable	Whole n=432 (100%)	AT* n=164 (38%)	NAT $ n=268 (62%)	*p*-value
Age (mean ± SD)	46.11 ± 11.98	48.00 ± 12.27	43.00 ± 10.83	<0.001§
Female (%)	95.10	94.80	95.70	0.819¥
Education				
Elementary school (%)	2.10	2.70	1.20	0.493¥
Middle school (%)	18.60	18.60	18.50	1.00¥
High school (%)	49.20	47.90	51.20	0.489¥
Graduate (%)	30.10	30.80	29.0	0.746¥
HADS (mean ± SD)	17.62 ± 7.50	16.44 ± 7.47	19.53 ± 7.2	<0.001§
Medication adherence scale				
GMAS (mean ± SD)	40.07 ± 4.46	41.62 ± 2.60	37.53 ± 5.57	<0.001§
MMAS-8 (mean ±S D)	8.15 ± 2.40	9.27 ± 1.73	6.32 ± 2.21	<0.001§

*Patients with a MASRI ≥80%; $Patients with a MASRI <80%; §Mann-Whitney U-test; ¥Chi-square test. GMAS: General Medication Adherence Scale; HADS: Hospital Anxiety and Depression Scale. MMAS-8: Morisky Medication Adherence Scale.

Table II. Patient-related barriers associated with adherence to therapy (AT) (OR<1) *vs*. non-adherence to therapy (NAT).

Barriers to therapy intake	Fisher's exact t-test		Multivariable*	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Therapy inclusion in routine	0.12 (0.05-0.28)	<0.001	0.09 (0.03-0.22)	<0.001
Difficulty in following the treatment plan	N/A$	<0.001	N/A$	-
Changes in daily routine	5.29 (2.94-9.54)	<0.001	4.84 (2.66-8.82)	<0.001
Forgetting to bring medications.	11.56 (3.36-39.75)	<0.001	11.69 (3.34-40.86)	<0.001
Feeling hassled	4.85 (2.25-10.45)	<0.001	4.04 (2.02-9.59)	<0.001
Feeling negative emotions	2.72 (1.41-5.25)	0.004	2.41 (1.23-4.71)	0.010
Perceiving therapy as a burden or stigma	3.04 (1.58-5.85)	0.001	2.65 (1.34-5.21)	<0.001
Unwanted reminder of own condition	2.49 (1.61-3.84)	<0.001	2.34 (1.50-3.66)	<0.001
Doubt about therapy efficacy	1.91 (1.02-3.58)	0.049	1.79 (0.93-3.45)	0.085

*Barriers statistically associated with non-adherence according to Fisher's exact test were analysed by multivariable logistic regression, adjusting each variable for age and gender; statistical significance was set at $p<0.05$.
$Difficulty in following the treatment plan was not recorded in any adherent patient.
CI: confidence interval; NA: not applicable; OR: odds ratio.

Results

Patients and their AT

This cross-sectional study comprised 432 adult Italian patients with SLE. The questionnaire response rate was 100%. Most patients were female (95.1%) and the mean age was 46.11±11.98 years (Table I). Of the 432 patients, 268 (62%) were AT (MASRI ≥80%), and 164 (38%) were NAT (MASRI <80%). The mean age was significantly higher in AT than in NAT ($p<0.001$). The items 'gender' ($p=0.819$) and "education" were similarly distributed between the AT and NAT groups, irrespective of the educational degree achieved (Table I). NAT patients reported significantly higher HADS scores than AT ($p<0.001$). Unsurprisingly, the AT GMAS and MMAS-8 mean scores were statistically higher in AT than in NAT ($p<0.001$).

Patient-related barriers to AT

As expected, the percentage of patients able to incorporate therapy into a daily routine was significantly higher in the AT than the NAT group (97% *vs*. 80.4%; OR=0.12, $p<0.001$), who also reported difficulties in following the treatment plan ($p<0.001$) (Table II). Additional practical barriers to AT were: changes in daily routine (OR=5.29, $p<0.001$) and forgetting to bring medications when traveling or leaving the house (OR=11.56, $p<0.001$). The perceived barriers were: feeling

hassled (OR=4.85, $p<0.001$), feeling negative emotions while following the treatment plan (2.72, $p=0.004$), perceiving therapy as a burden or stigma (OR=3.04, $p=0.001$) or as an unwanted reminder of their condition (OR=2.49, $p<0.001$); and doubting whether the correct intake of therapy really prevents worsening of their clinical condition (OR=1.91, $p=0.049$). Then, a multivariable analysis was performed to evaluate whether the associations between NAT and barriers (found to be statistically significant at Fisher's exact test) were influenced by age and/or gender. After adjustment for confounding variables, the only association lost between NAT and AT was doubting that a correct therapy could prevent worsening of their clinical condition. The same result was obtained when the multivariable analysis was repeated including 'age' as single confounding variable, while the association remained statistically significant with 'gender' (data not shown), suggesting that age may play a more significant role in influencing patients' beliefs about treatment effectiveness and their adherence behaviour.

Therapy-related barriers to AT

The percentage of patients, reporting difficulties in taking the prescribed medications, were significantly higher in the NAT than the AT group (7.4% *vs*. 0.8%; OR=10.44, $p<0.001$), as was the percentage of NAT patients stopping medications without informing the doctor (6.6% *vs*. 1.6%; OR=4.47, $p=0.010$) (Table III). The practical barriers found significantly different between groups were: 1) reducing or stopping medications because of side effects, without informing the doctor (OR=5.73, $p<0.001$) and; 2) missing due to disease progression and the addition of new medication (OR=4.78, $p<0.001$). At variance with the NAT group, none of the AT patients discontinued medication when feeling well ($p<0.001$). The perceived barriers related to medication were: 1. fear of side effects (OR=29.15, $p<0.001$) and 2. believing some prescriptions unnecessary (OR=4.23, $p=0.015$). All the associations remained statistically significant after adjusting each for age and gender at multivariable analysis.

Table III. Therapy-related barriers associated with adherence to therapy (AT) (OR<1) *vs*. non-adherence to therapy (NAT).

Barriers to therapy intake	Fisher's exact t-test		Multivariable*	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Difficulties in taking the prescribed medication	10.44 (2.30-47.27)	<0.001	10.92 (2.37-50.28)	0.002
Stopping taking medications without informing the doctor	4.47 (1.37-14.51)	0.010	4.37 (1.27-14.97)	0.019
Side effects	5.73 (2.05-16.00)	<0.001	5.67 (1.96-16.39)	0.001
Disease progression and addition of new medication	4.78 (1.94-11.78)	<0.001	5.65 (2.20-14.45)	<0.001
Discontinuing medications when feeling well	N/A[$]	<0.001	N/A[$]	-
Fear of side effects	29.15 (3.82-222.25)	<0.001	29.9 (3.86-231.32)	0.001
Believing some prescriptions unnecessary	4.23 (1.96-11.78)	0.015	3.96 (1.79-8.75)	0.001

*Barriers statistically associated with non-adherence according to Fisher's exact test were analysed by multivariable logistic regression, adjusting each variable for age and gender; statistical significance was set at $p<0.05$.
[$]Discontinuing medications when feeling well was not recorded in any adherent patient.
CI: confidence interval; NA: not applicable; OR: odds ratio.

Table IV. Socioeconomic- and healthcare system-related barriers associated with adherence to therapy (AT) (OR<1) vs non-adherence to therapy (NAT).

Barriers to therapy intake	Fisher's exact t-test		Multivariable*	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Social-related				
High cost	3.75 (1.58-8.90)	0.002	3.68 (1.51-8.98)	0.004
Healthcare system-related				
Long waiting list	1.69 (1.14-2.52)	0.010	1.90 (1.25-2.87)	0.002
Believing that long waiting list interferes with therapy intake	2.01 (1.28-3.15)	0.003	2.13 (1.33-3.35)	0.002
Conflictual opinions between specialists on therapy	2.10 (81.37-3.21)	0.001	2.09 (1.34-3.24)	0.001
Prescribing delay	2.36 (1.35-4.11)	0.004	2.14 (1.21-3.79)	0.009
Information on mechanisms of drug action	0.47 (0.32-0.71)	<0.001	0.43 (0.28-0.66)	<0.001
Poor communication with the healthcare system staff	1.64 (1.10-2.44)	0.017	1.64 (1.09-2.47)	<0.001
Discontinuity in the interest regarding their case	1.78 (1.19-2.64)	0.005	1.90 (1.25-2.87)	0.002

*Barriers statistically associated with non-adherence according to Fisher's exact test were analysed by multivariable logistic regression, adjusting each variable for age and gender; statistical significance was set at $p<0.05$.
CI: confidence interval; NA: not applicable; OR: odds ratio.

Socioeconomic-and healthcare system-related barriers to AT

Among barriers in the socioeconomic domain (listed in supplementary data), the only one that was statistically different between NAT and AT was the difficulty in buying medicines due to their cost (OR=3.75, $p=0.002$). In the healthcare system domain, statistically different practical barriers were: 1. the long waiting times between follow-up visits (OR=1.69, $p=0.010$), which are believed to affect the intake of the prescribed therapy (OR=2.01, $p=0.003$); 2. conflicting opinions from different specialists about medication (OR=2.10, $p=0.001$); interruption of therapy due to delay in the prescription of medications (OR=2.36, $p=0.004$). Furthermore, a lower percentage (49.7% *vs*. 67.4%) of NAT patients reported receiving adequate information about how the prescribed medication works (OR=0.47, $p<0.001$). Also, NAT patients felt they had poor communication with the healthcare system staff (OR=1.64,

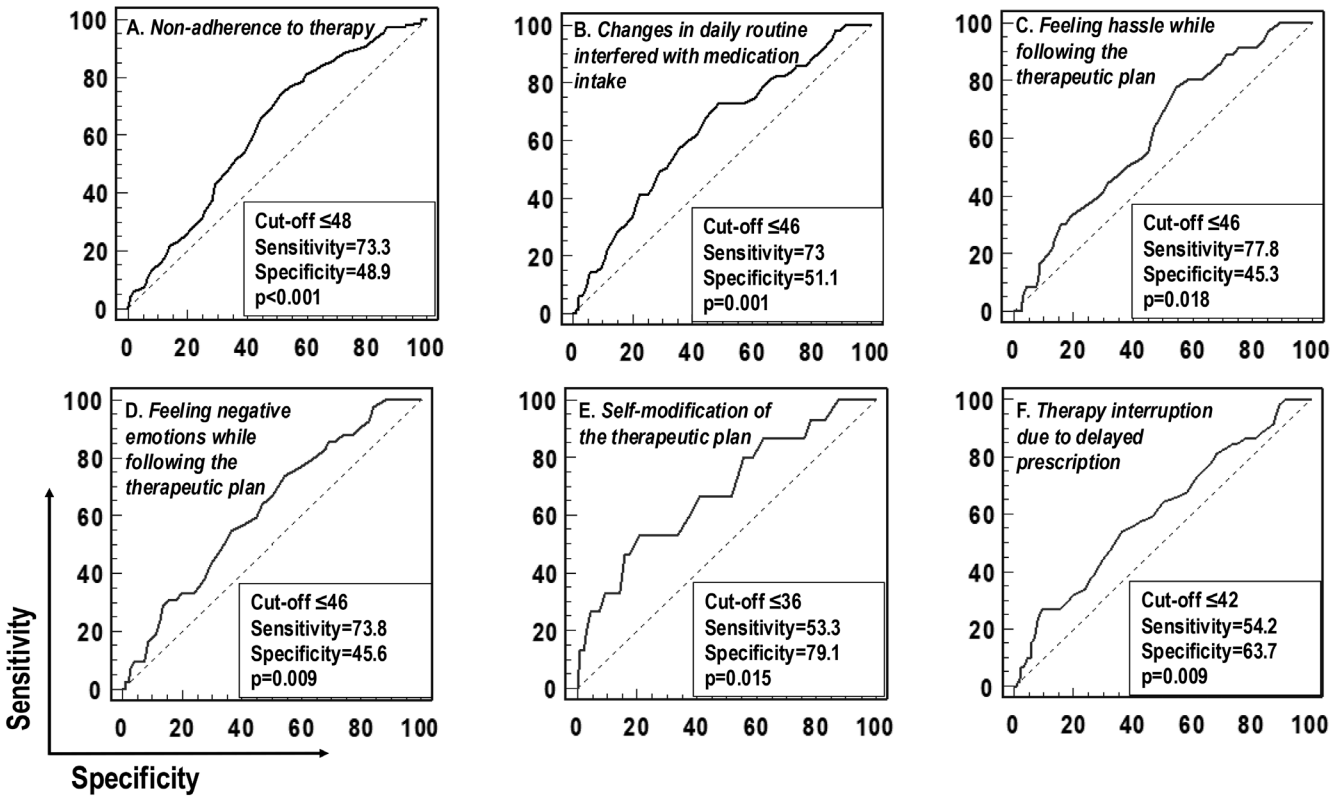

Fig. 1. Receiver operating characteristic (ROC) analysis to define cut-off age distinguishing patients according to non-adherence to therapy (NAT) and its barriers. For each ROC curve, age was the predictor variable and the parameter indicated in each panel represented the outcome.
A: NAT *vs*. AT patients. **B**: Changes in daily routine interfered with medication intake *vs*. did not interfere. **C**: Feeling hassled while following the therapeutic plan *vs*. not feeling hassled. **D**: Feeling negative emotions while following the therapeutic plan *vs*. not feeling them. **E**: Modifying the therapeutic plan *vs*. not modifying it. **F**: Interrupting therapy due to a delay in medication prescription *vs*. not interrupting therapy.

p=0.017) and encountered discontinuous interest (OR=1.78, p=0.005).

Association between age and barriers to AT

Given the difference in mean age between AT and NAT patients, the potential role of age in contributing to NAT and specific adherence barriers was investigated. Specifically, ROC analyses were performed to identify age cut-offs able to distinguish patients according to NAT status and related barriers (Fig. 1). The optimal age cut-off distinguishing NAT from AT was ≤48 years, with a sensitivity of 73.3% and specificity of 48.9% (p<0.001; Fig. 1A). A similar cut-off (≤46 years) was identified among patients reporting changes in daily routine interfering with medication intake (sensitivity 73.0%, specificity 51.1%, p=0.001; Fig. 1B), feeling hassled (sensitivity 77.8%, specificity 45.3%, p=0.018; Fig. 1C), and feeling negative emotions (sensitivity 73.8%, specificity 45.6%, p=0.009; Fig. 1D) while following the therapeutic plan. A lower age cut-off of ≤36 years was significantly associated with self-modification of the therapeutic plan (sensitivity 53.3%, specificity 79.1%, p=0.015; Fig. 1E), while an age cut-off of ≤42 years was associated with therapy interruption due to delays in the prescription of medications (sensitivity 54.2%, specificity 63.7%, p=0.009; Fig. 1F). These findings suggest that younger age may be a significant risk factor for both general NAT and specific behavioural and emotional barriers to adherence.

Discussion

This is the first study to investigate the prevalence of barriers to AT in a large cohort of Italian patients with SLE, using a comprehensive self-administered questionnaire. Wide ranges of non-adherence to therapy (NAT) rates have been reported across countries (3–75%), reflecting differences in study design, cultural factors influencing adherence, healthcare system characteristics, and the adherence assessment tools used (15).

We found that the NAT rate, according to MASRI, was 38%, which aligns with MASRI-based NAT rates reported internationally, ranging from 7.7% in France (16) to up to 51.1% in USA (11). The strong correlation found between MASRI scores, MMAS-8 and GMAS AT scales in our study population, reinforce the reliability of our data. We found a significant difference in age between AT and NAT patients, non-adherent individuals being younger. This finding is in line with previous studies showing that older age is associated with better AT (17, 18). Specifically, a cross-sectional study involving 157 Mexican SLE patients demonstrated that older age was protective against NAT (17). Moreover, a prospective study carried out among 172 Thai patients with SLE found that older age was associated with greater AT (18). Similarly, an international, prospective, observational multicentre study involv-

ing 305 patients with flaring SLE found associations between lower age at inclusion and at diagnosis and NAT. In a longitudinal American study involving more than 10,000 Medicaid beneficiaries with SLE study, younger age exhibited a significant association with both NAT and a declining AT (6). Likely causes of the association between younger age and poor AT are irregular routines and/or a lower awareness of health risks. However, some studies have found no significant association between age and AT in SLE (19, 20), suggesting that other factors, such as social and psychological characteristics, may also influence AT.

Similarly to previous studies (18, 20, 21), gender did not appear to influence AT in our cohort, probably because of the limited prevalence of male patients. No differences in education levels were found between AT and NAT patients, although literature has shown conflicting results on this aspect across different populations. Indeed, while some studies suggested that higher education levels are associated with better AT (20, 22) others indicated that patients with higher education might more frequently question and adjust their treatment plans, or forget medication due to time constraints associated with their professional responsibilities (23).

The inverse correlation between AT and psychological distress, as measured by HADS, is consistent with previous findings suggesting that anxiety and depression are key determinants of poor AT in chronic diseases, including SLE (24).

Patient-related barriers significantly influenced AT in our cohort. Specifically, NAT patients more frequently reported difficulty in integrating therapy into daily routines because of changes in daily routine and forgetfulness when leaving home. These findings are consistent with previous reports indicating that the complexity of daily life in chronic illness often affects AT (11). As in previous studies, perceived barriers, such as finding treatment burdensome, experiencing negative emotions while following the regimen, and viewing therapy as a stigma or an unwelcome reminder of illness, also emerged as important determinants of NAT (2, 25).

Among therapy-related barriers, fear of side effects showed the strongest association with NAT. This is consistent with previous studies that defined fear of adverse effects as a leading cause of intentional NAT in SLE and a reliable predictor of treatment discontinuation (15, 26). In addition, a significant number of NAT patients reported that they reduced or discontinued therapy without informing the physician because of side effects, indicating that actually experiencing side effects also plays a crucial role. These findings underline the importance for healthcare providers to discuss potential side effects and outline realistic expectations.

Similarly to previous reports, none of the AT patients reported discontinuing medication when feeling well, suggesting that perceived disease quiescence is a key factor in intentional NAT. Previous studies have also shown that patients often stopped medications when feeling better, underestimating the risk of flare-ups (27).

Similarly to previous reports (19, 27), we found that discontinuing medication during perceived wellness periods and the belief that not all prescribed drugs are necessary are both relevant intentional NAT barriers. For instance, in our cohort, none of the AT patients reported discontinuing medication when feeling well, while a high proportion of NAT patients believed some prescriptions unnecessary. These findings underscore the importance of patient education regarding the chronic nature of SLE and the role of maintenance therapy in preventing disease flares, even during periods of apparent remission.

In our cohort, missing medications due to disease progression and subsequent polypharmacy was significantly more prevalent among NAT individuals. This finding aligns with prior literature indicating that increases in medication complexity – particularly in the context of active or flaring disease – can compromise AT (28, 29).

From a socioeconomic and healthcare system perspective, difficulty in affording medications was the only socioeconomic barrier significantly associated with NAT. By contrast, several healthcare system-related barriers were identified, including long waiting times between follow-up visits, divergent medical opinions among specialists, and delays in prescription renewals. Moreover, NAT patients more frequently reported poor communication and a perceived lack of continuity or interest by healthcare providers. These findings are in line with previous studies demonstrating that healthcare system-related barriers, such as accessibility, efficiency, and communication, play a critical role in impacting AT among patients with SLE (2, 4, 27). Strengthening the healthcare system in these areas could substantially enhance AT, prevent disease flares, and improve long-term outcomes for patients with SLE.

Altogether, our findings underscore the need for multidimensional strategies to enhance AT in patients with SLE. These should incorporate educational interventions, psychological support, simplification of treatment regimens, and improved physician-patient communication strategies. Given the significant association between younger age and both overall NAT and specific behavioural and emotional barriers, targeted interventions should be directed toward patients aged 46 years and younger. By adopting such a focused strategy, physicians can play a crucial role in identifying and managing the distinct barriers younger patients encounter, which may reduce their risks and enhance adherence outcomes.

This study has several limitations. Firstly, the cross-sectional design precludes causal inference between identified barriers and NAT. Secondly, reliance on self-report measures for AT, including the MASRI, may have introduced recall or social desirability bias, as patients could have provided responses that were more compliant than their actual behaviour. Thirdly, the absence of objective AT measures (*e.g.* pharmacy refill data, serum drug levels) limits external validation of self-reported behaviour. Finally, as clinical data were available for only a subset of patients, this precluded assessment of potential associations between AT and disease activity, flares, and/or specific organ involvement, none of them included in MASRI. Despite these limitations, our study

provides valuable insights into the multifactorial barriers to AT in Italian SLE patients. Future longitudinal studies are needed to assess the impact of targeted interventions on AT and to elucidate the underlying causal mechanisms.

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