

Patients with recent-onset systemic lupus erythematosus use more antidepressant medication than matched controls

A case–control study

Simo Kariniemi, MD, PhD^{a,*}, Pia Elfving, MD, PhD^{a,b}, Lauri J. Virta, MD, PhD^c, Hannu Kautiainen, BA^{d,e}, Kari Puolakka, MD, PhD^f, Vappu Rantalaiho, MD, PhD^{g,h,i}

Abstract

Systemic lupus erythematosus (SLE) is associated with mental health concerns. We evaluated the quantity, frequency, and risk of antidepressant and antipsychotic medication use associated with recent-onset SLE in a case–control study. SLE patients were identified by their drug reimbursement decisions for SLE medication made during January 1, 2000 to December 31, 2014 from the register of the Social Insurance Institution. The study included 1006 SLE cases and 3005 controls. The information about new purchases of the antidepressants and antipsychotics was retrieved from the National Drug Purchase Register starting 1 year before the reimbursement decision (index day [ID]) until 5 years after the ID, death or December 31, 2015. The defined daily dose (DDD) was used to measure the drug consumption. During the 12 months before the ID, the mean daily antidepressant consumption was 62.3 DDDs and 57.9 DDDs ($P < .001$) for patients and controls, respectively. The mean antidepressant consumption rose to 87.3/1000/day in patients and 77.4/1000/day in controls ($P < .001$) during the 5-year period after the ID. The adjusted hazard ratio for purchasing antidepressants was 1.45 (95% confidence interval: 1.19–1.77; $P < .001$) for patients compared to controls. No significant difference was found between patients and controls concerning antipsychotics. An increase in antidepressant use was found among SLE cases, suggesting the presence of mood disorders already at the time of SLE diagnosis. No difference was recorded in the use of antipsychotics, indicating the rarity of chronic psychotic disorders needing long-term antipsychotic treatment in SLE.

Abbreviations: ATC-classification = Anatomical Therapeutic Chemical Classification, CI = confidence interval, DDD = defined daily dose, FBBP = Finnish Pharmaceuticals Pricing Board, HR = hazard ratio, ID = index day, SD = standard deviation, SII = Social Insurance Institution, SLE = Systemic Lupus Erythematosus, WHO = World Health Organization.

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^a Department of Medicine, Kuopio University Hospital, Kuopio, Finland, ^b Institute of Clinical Medicine, University of Eastern Finland, Kuopio, Finland, ^c Research Department, Social Insurance Institution, Helsinki, Finland, ^d Primary Health Care Unit, Kuopio University Hospital, Kuopio, Finland, ^e Folkhälsan Research Center, Helsinki, Finland, ^f Terveystalo Healthcare, Lappeenranta, Finland, ^g Faculty of Medicine and Health Technology, Tampere University, Tampere, Finland, ^h Centre for Rheumatic Diseases, Tampere University Hospital, Tampere, Finland, ⁱ Kanta-Häme Central Hospital, Hämeenlinna, Finland.

* Correspondence: Simo Kariniemi, Department of Medicine, Kuopio University Hospital, P.O. Box 100, 70029 KYS Kuopio, Finland (e-mail: simo.kariniemi@gmail.com).

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1. Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease, which can affect multiple organs. It is associated with several comorbid conditions, such as cardiovascular diseases, infections, malignancies, and renal diseases. These comorbidities have a crucial effect on the daily living of SLE patients and therefore, paying attention to these problems is essential when managing SLE in a holistic way. Although mental health concerns may often remain unrecognized in daily practice, they form a marked comorbidity among SLE patients as well.^[1–12] In SLE, the occurrence of mood disorders may be due to numerous factors, such as the burden of chronic disease, immunological factors, and medication.^[1,2,4,7,8] In addition, SLE can sometimes manifest as psychosis, and psychiatric symptoms may develop as an adverse effect of glucocorticoid (GC) treatment.^[5,6,8] Although multiple studies have explored the occurrence of mental health concerns in SLE, there is a clear lack of comparative studies considering the actual risk of these problems among patients. In addition, the number of case–control studies assessing antidepressant and antipsychotic medication use and its risk among SLE patients is limited.^[2–4,9–12] Thus, the aim of this study was to explore the quantity, frequency and risk of antidepressant and antipsychotic medication use associated with recent-onset SLE. We hypothesized that antidepressant and antipsychotic drug use would be more common among recent-onset SLE patients than among their matched controls.

2. Materials and methods

2.1. Patients and controls

Every resident in Finland is legally entitled to national health insurance and Finnish Social Insurance Institution (SII) holds a register of these insurances. People who have chronic rheumatic diseases have a right to special (higher than usual) compensation for anti-rheumatic drugs in Finland.

Recent-onset SLE patients (age > 17 years) were identified based on new reimbursements for SLE medication granted by the SII during January 1, 2000 to December 31, 2014. The reimbursement decisions were based on the 10th International Classification of Diseases code M32. The application for reimbursement is made by a specialist in rheumatology or a physician working in such clinic based on general recommendations on managing SLE, such as European League Against Rheumatism or American College of Rheumatology guidelines. In Finland, the reimbursements for SLE medication are granted within approximately 3 weeks after the reimbursement application has been made (i.e., after SLE is diagnosed).

For each patient, 3 controls were randomly selected from the Population Register Centre of Finland. The controls were individually matched to SLE cases regarding age, sex, and place of residence at the index day (ID). The ID was defined as the date when the reimbursement for SLE medication was granted by the SII. Unfortunately, the study lacked data on ethnicity. However, almost all residents in Finland are White people, as the immigration rate has been low.^[13]

2.2. The observation and follow-up time

The information about the purchases of the antidepressant and antipsychotic medication was retrieved from the National Drug Purchase Register of Finland from the beginning of 1999 to the end of 2015. For each patient, the observation time for purchasing these drugs started 12 months before the ID and the follow-up started from the ID. They both lasted until 5 years after the ID, the patient died, or until December 31, 2015, whichever occurred first. Six-month time frames were used in the analyses.

As we wanted to assess the drug purchases used for the management of mental health concerns associated with recent-onset

SLE, the patients (and their purchases) who had purchased these drugs before the observation time, were excluded from the analyses. Otherwise, a patient was considered to use the drug if she/he had purchased it at least once during the observation time. We also examined the cumulative shares of new antidepressant purchasers. From this analysis, we excluded all the patients who had purchased antidepressant drug therapy before the ID.

2.3. Drugs

In Finland, drug purchases are recorded in detail according to the Anatomical Therapeutic Chemical Classification (ATC-classification) System (code, amount, date) in the Drug Purchase Register maintained by SII. The drug compensation system is divided into 3 levels: a basic rate of reimbursement, a lower special rate of reimbursement and a higher special rate of reimbursement defined by the SII. However, the Drug Purchase Register does not contain the indication of the drug for which it has been purchased.^[14,15]

The ATC codes N06A (antidepressants) and N05A (antipsychotics) were used to detect antidepressant and antipsychotic drug purchases. These drug groups are recommended by the Finnish Current Care guidelines when managing patients with depression and/or schizophrenia in Finland. Finnish Current Care guidelines are evidence-based clinical practice recommendations developed by the Finnish Medical Society Duodecim. These national guidelines consider important issues on management and prevention of diseases in Finland including rheumatoid arthritis, asthma, depression, and others.^[16–18]

To a drug product to receive the reimbursement entitlement, the pharmaceutical company must make an application for the Finnish Pharmaceuticals Pricing Board (FBBP). After reviewing the application, the FBBP may grant an entitlement for the drug according to indication, package size and strength. The entitlement is re-checked monthly afterwards. Lists of drug products with an entitlement are available at FBBP's website in Finnish.^[19]

The purchases of antidepressants were further evaluated at group level: nonselective monoamine reuptake inhibitors (N06AA), selective serotonin reuptake inhibitors (N06AB), monoamine oxidase A inhibitors (N06AG), and other antidepressants (N06AX).^[14] To measure the drug consumption, we used the defined daily dose (DDD) described by the World Health Organization. DDD is the assumed average maintenance dose per day for a drug used for its main indication for adults, and it provides a fixed unit of measurement that accounts for the differences in medicine formulations, package sizes and strengths. Thereby, DDD enables international comparisons at the population level.^[20]

2.4. Ethical aspects

Since this study was register-based and done without contacting patients, neither approval of an ethical committee nor patients' informed consent were required by Finnish law. The approval to use these registers was acquired from the register holders, that is, SII (document number: 74/522/2013) and Population Register Centre (document number: 2168/410/13).

2.5. Statistical methods

The characteristics are presented as means with standard deviation (SD) for continuous variables and as frequencies with percentages for categorical variables. Statistical comparison between groups for the consumption of antidepressants (DDD) was made by using the Mann–Whitney test. Longitudinal measures of purchases of antidepressants were analyzed using generalized estimating equations models with the unstructured correlation structure and binomial link function; the models include the main effects of groups and

periods and their interaction. The Kaplan–Meier curve was used to illustrate the cumulative proportions of new antidepressant purchasers. The Cox proportional hazards regression was used to estimate the adjusted hazard ratios (HRs) and their 95% confidence intervals (CIs). Stata 17.0 (StataCorp LP, College Station, TX) was used for the statistical analyses. The data of this study are not publicly available due to sensitivity but are available from the corresponding author on reasonable request.

3. Results

The study consisted of 1006 SLE patients (84% females) and 3005 controls. At the time of ID, mean age was 44.9 (SD 15.9) years in females and 48.6 (SD 16.4) years in males. A total of 264 (26%) patients (88% females) and 571 (19%) controls (89% females) had at least 1 new purchase of antidepressant medication during the observation time.

During the 12 months before the ID, the mean daily antidepressant consumption was 62.3 DDDs and 57.9 DDDs ($P < .001$) for SLE patients and their controls, respectively. During the 5-year period after the ID, the mean antidepressant consumption rose to 87.3 DDDs in patients and to 77.4 DDDs in controls ($P < .001$).

In females with SLE, the proportions of new antidepressant purchasers were significantly higher than in controls almost throughout the entire observation time (Fig. 1). Depending on

the time of inspection, the differences ranged roughly from 1% to 3% points. The percentage of purchasers among females with SLE was at its highest 1 year after the ID (almost 12%), but the share decreased over time and returned to the same level as 12 months before the ID (closely 9%). On the contrary, no significant difference was found in males at any inspection point (Fig. 2). When sexes were compared, 27.6% of females and 19.3% of males with SLE had purchased antidepressants ($P = .028$). The difference between sexes was also found among controls, since 20.0% of females and 13.5% of males had purchased antidepressants ($P = .001$).

The cumulative proportions of new antidepressant purchasers are presented in Figure 3. Five years after the ID, 18.7% (95% CI: 16.1–21.7%) of patients and 13.5% (95% CI: 12.2–15.0%) of controls had purchased antidepressants at least once during the follow-up. The age- and sex-adjusted HR for purchasing antidepressant medication was 1.45 (95% CI: 1.19–1.77; $P < .001$) for patients compared to controls.

Selective serotonin reuptake inhibitors were the most popular antidepressant group in both SLE patients (47.7%) and controls (53.7%). No significant difference was found between patients and controls in relation to distribution of the purchased antidepressant types (Table 1).

Concerning the purchasers of antipsychotic drug therapy, there was no significant difference between SLE patients and their controls. The share of new antipsychotic purchasers during the observation time was 2.5% (95% CI: 1.7–3.3) among

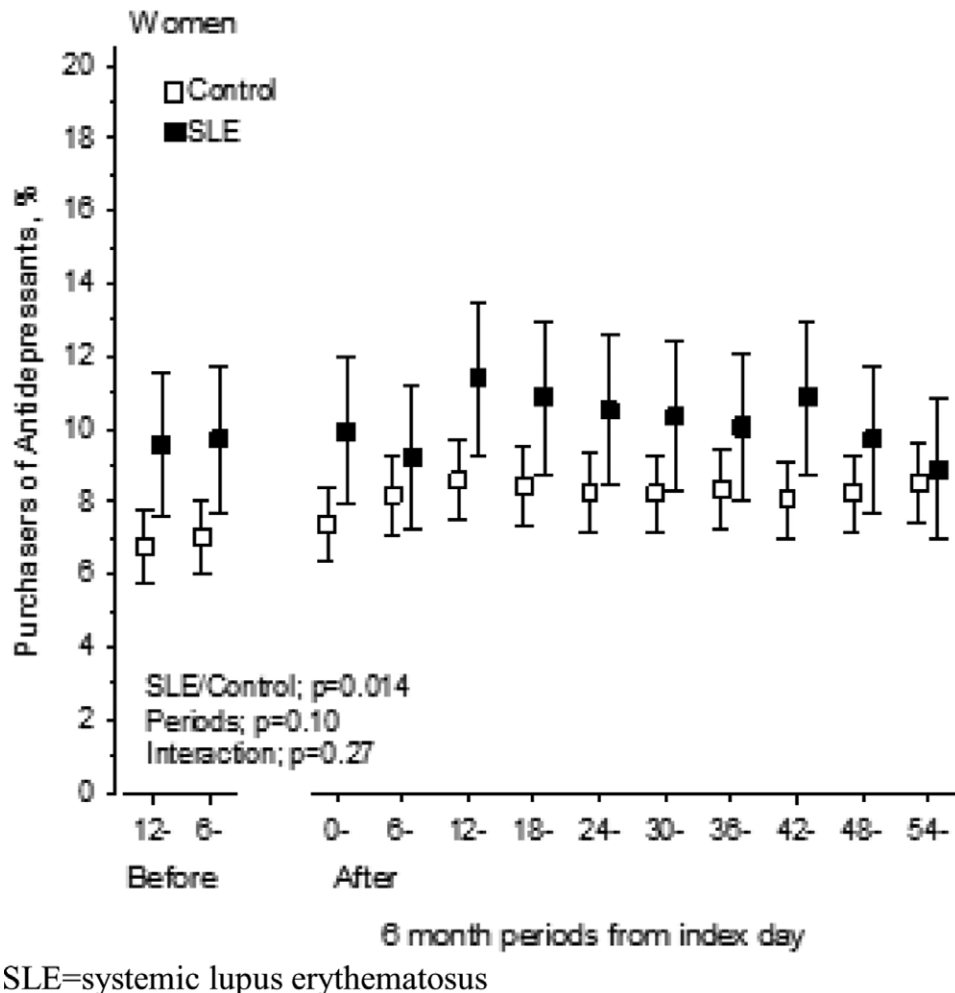
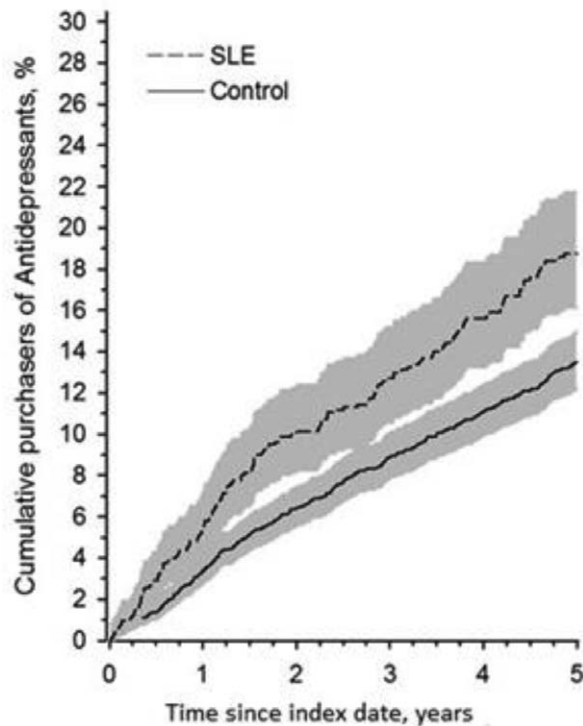


Figure 1. The proportion of new antidepressant drug purchasers among female patients with recent-onset systemic lupus erythematosus and their matched controls in Finland between 12 months before the index day and 60 months after the index day, death, or the end of the year 2015. Data collected from 1999 to 2015.

Notably, the use of antidepressants was increased earlier than SLE was diagnosed. We assume that this finding may reflect the association of early SLE and mood disorders. Interestingly, a similar trend was observed in another Finnish study, which evaluated the use of drugs used for cardiovascular diseases.^[21] Moreover, other studies have reported that the risk of multiple morbidities is already higher before SLE is diagnosed compared to matched controls, and mood disorders seem to be no exception.^[10,11] These results indicate that the risk of comorbid conditions is increased in early SLE.^[10,11,21] The elevated risk of comorbidities may be associated with systemic inflammation and slow development of SLE. In addition, SLE diagnosis is often delayed by years.^[11,22,23] On the other hand, mood disorder may also be a sign of a neuropsychiatric component of early SLE.^[1,24,25] However, at least 1 study has shown that depressive individuals and antidepressant medication users had an increased risk for developing SLE, which may suggest that prior depression might be associated with the risk of SLE development.^[26]

We also observed that the shares of new antidepressant purchasers did not differ between patients and controls among



SLE=systemic lupus erythematosus

Figure 3. Cumulative purchasers of new antidepressant medication among recent-onset systemic lupus erythematosus patients and matched controls in Finland during the first 5 years after the index day. Data collected from 2000 to 2015.

females at the end of the follow-up. Although the issue is complex, it would be tempting to conclude that the started SLE management would have decreased disease activity and severity of SLE and thereby eased mood disorders secondary to active SLE and its symptoms.^[4,27-30]

However, some of the antidepressants, such as duloxetine, mirtazapine, and amitriptyline may be used for multiple indications including mood disorders and chronic pain. Depression, anxiety, sleeping difficulties and chronic pain are also known to be closely interconnected. Thereby, we cannot rule out that some of the antidepressants were used for management of other health concerns than mood disorders in this study.^[31-35]

We also found that the antidepressant consumption appeared to increase over time among controls. The finding is likely explained by the increased prevalence of depression and the increase in the use of antidepressant medication over time in general in Finland like nationwide studies have presented.^[36,37]

Our other aim was to study the long-term need of antipsychotics in recent-onset SLE by looking at antipsychotic drug purchasers. Therefore, we analyzed all new antipsychotic drug purchasers treated in both primary and specialized care. Contrary to our expectations, we observed no significant difference in the use of these drugs between SLE patients and their controls.

Psychoses and psychotic disorders occur rarely in SLE. However, in many cases they require antipsychotic drug therapy to alleviate the symptoms.^[3,5,6,8,10,11,38,39] For example, a study from the United Kingdom examined only psychoses related to SLE and followed around 700 SLE patients diagnosed between 1978 and 2018. They described that 2.5% of the patients experienced psychosis during a mean follow-up of 18 years. Around 40% of the patients were taking antipsychotic medication, but the duration of treatment was not reported in the study.^[5] In addition, Hanly et al studied nearly 2000 patients with SLE recruited in 1999 to 2011. Only 1.5% of them experienced at least 1 psychotic event during a mean of 7 years of follow-up, but almost 70% of SLE cases with psychosis needed antipsychotic medication during the study.^[6] Furthermore, a Thai study examined more than 700 SLE patients between 1999 and 2009 and described that 5 percent of them had at least 1 psychotic episode. All patients needed antipsychotic drugs, while the mean duration of treatment was only 2 to 3 months.^[39] Thus, our results on the consumption of antipsychotics can be explained by the facts that psychosis is an infrequent manifestation of SLE, no increased risk of chronic psychotic disorders appears to exist in SLE, and the need for antipsychotic treatment seems to be only temporary. Moreover, a glucocorticoid-induced psychosis seems to be a rare complication with a favorable outcome in SLE.^[3,5,6,8,38-40]

The strengths of this study are the case-control study design and the long observation time. Furthermore, we used extensive nationwide information derived from official registers with high quality and included both primary and specialized health care patients. In addition, we evaluated the use

Table 1

The number and proportion of the purchased antidepressants by subgroups according to Anatomical Therapeutic Chemical Classification and compared to all purchased antidepressants in recent-onset systemic lupus erythematosus patients and matched controls in Finland between 12 months before the index day and 5 years after the index day, death, or the end of the year 2015. Data collected from 1999 to 2015.

Antidepressant group	Controls N (%)	SLE patients N (%)
Nonselective monoamine reuptake inhibitors (N06AA)	75 (10.2)	55 (16.0)
Selective serotonin reuptake inhibitors (N06AB)	395 (53.7)	164 (47.7)
Monoamine oxidase A inhibitors (N06AG)	6 (0.8)	5 (1.4)
Other antidepressants (N06AX)	259 (35.2)	120 (34.9)

N = number, SLE = systemic lupus erythematosus.

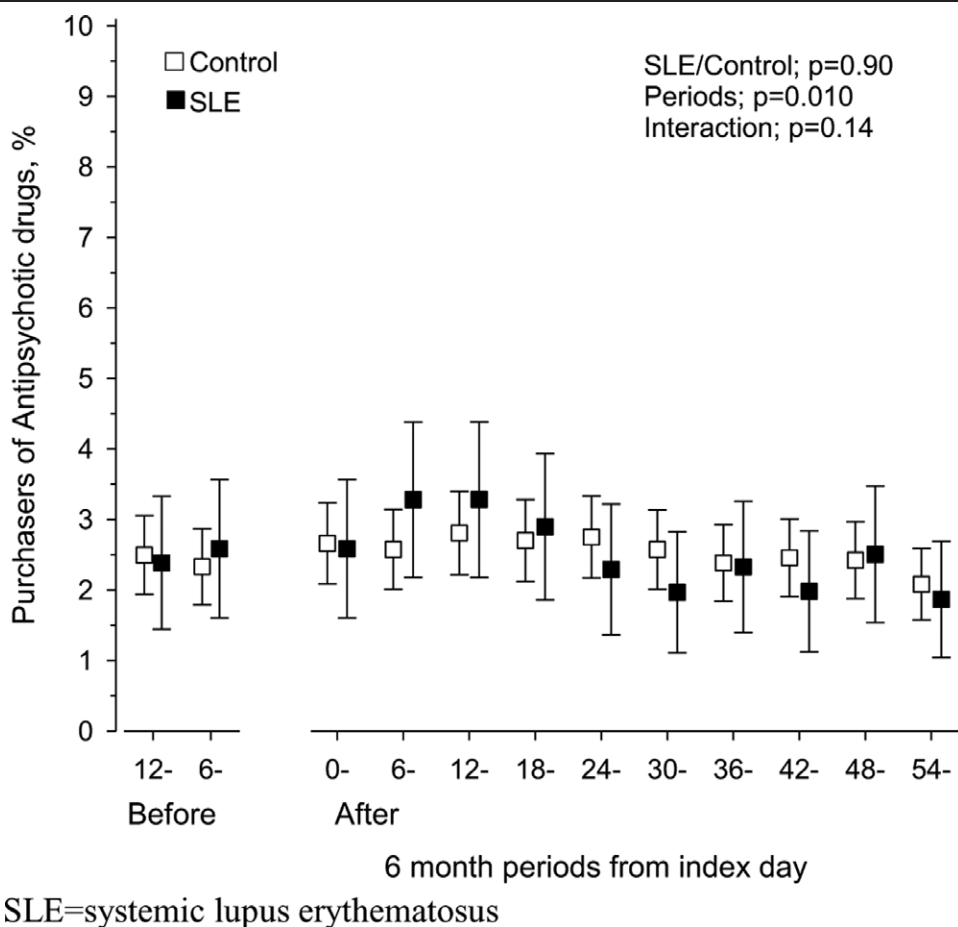


Figure 4. The proportion of new antipsychotic drug purchasers among patients with recent-onset systemic lupus erythematosus and their matched controls in Finland between 12 months before the index day and 60 months after the index day, death, or the end of the year 2015. Data collected from 1999 to 2015.

of antidepressant and antipsychotic drug therapy based on data on purchases obtained from the National Drug Purchase Register, which depicts the use more accurately than evaluation of prescriptions.

The limitations of this study are the lack of clinical data and the retrospective study design. Therefore, the severity of SLE or possible mental health concerns could not be determined, nor was the association of severity with antidepressant and antipsychotic medication. We also lacked data on possible previous mental health concerns and SLE medications on different manifestations. In addition, some of the drugs may be used for other purposes, such as to treat sleeping difficulties and neuropathic pain. As we did not have data on indications, we cannot make firm conclusions on the reasons behind the increased use of antidepressants.^[31–33] Lastly, we were not able to resolve the factors behind the temporal variation on antidepressant use. Therefore, future studies should be made to explain these phenomena.

5. Conclusions

Our nationwide study showed that SLE patients used slightly, albeit significantly, more antidepressants than their peers in the long term. We assume that this finding reflects the extent of mood disorders associated with SLE, which may exist early in the disease course. On the other hand, our results indicate the rarity of developing a chronic psychotic disorder that needs long-term antipsychotic drug therapy in SLE. Thus, it is recommended to screen for mood disorders already at the time of SLE diagnosis.

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Author contributions

- Conceptualization:** Simo Kariniemi, Pia Elfving, Lauri J Virta, Hannu Kautiainen, Kari Puolakka, Vappu Rantalaiho.
- Data curation:** Hannu Kautiainen, Kari Puolakka.
- Formal analysis:** Hannu Kautiainen.
- Funding acquisition:** Simo Kariniemi.
- Investigation:** Pia Elfving, Lauri J Virta, Hannu Kautiainen, Vappu Rantalaiho.
- Methodology:** Simo Kariniemi, Pia Elfving, Lauri J Virta, Hannu Kautiainen, Kari Puolakka, Vappu Rantalaiho.
- Project administration:** Simo Kariniemi, Pia Elfving, Kari Puolakka, Vappu Rantalaiho.
- Resources:** Kari Puolakka.
- Software:** Hannu Kautiainen.
- Supervision:** Pia Elfving, Kari Puolakka, Vappu Rantalaiho.
- Validation:** Pia Elfving, Vappu Rantalaiho.
- Visualization:** Simo Kariniemi, Hannu Kautiainen.
- Writing – original draft:** Simo Kariniemi.
- Writing – review & editing:** Simo Kariniemi, Pia Elfving, Lauri J Virta, Hannu Kautiainen, Kari Puolakka, Vappu Rantalaiho.

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