Beneficial Effects of Concomitant Long-Acting Injectable Antipsychotics on Time to Rehospitalization in Patients With Treatment-Resistant Schizophrenia Receiving Clozapine:

A Retrospective Cohort Study

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Abstract

Introduction: This study aimed to assess the association between long-acting injectable (LAI) antipsychotic prescription and the risk of psychiatric hospitalization in patients with treatment-resistant schizophrenia (TRS) receiving clozapine.

Methods: In this retrospective cohort study at a single tertiary psychiatric center, we analyzed rehospitalization hazard ratios (HRs) in refractory schizophrenia patients, classified by *DSM-IV-TR* and *DSM-5* criteria. We examined various psychotropic regimens—clozapine with or without other oral antipsychotics (OAPs) or LAI antipsychotics. Subgroups were stratified by daily clozapine dosage and previous admissions.

Results: A total of 719 patients were included in the study. Analyses were conducted on all the patients over 3-month, 6-month, and 1-year periods. Patients treated with a combination of clozapine and LAI antipsychotics (CLO + LAI) had a significantly higher number of previous hospitalizations ($P = .003$), and a higher daily dose of clozapine ($P < .001$) was found in the CLO + OAP group than in the CLO (monotherapy) group and the CLO + LAI group. Patients treated with LAI antipsychotic comedication had significantly lower HRs for rehospitalization in 1 year among 3 studied groups. Moreover, the protective effects of LAI antipsychotics were observed in all the subgroups stratified by daily clozapine dosage and number of previous admissions to represent disease severity.

Conclusion: The combination of clozapine and LAI antipsychotics was associated with a significantly lower risk of rehospitalization compared to both the combination of clozapine and OAPs and clozapine monotherapy. The use of LAI antipsychotics should be considered to prevent rehospitalization in patients with TRS who are already being treated with clozapine.

J Clin Psychiatry 2024;85(2):23m15071

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Schizophrenia, a chronic and heterogeneous disorder that presents as a combination of multiple psychotic symptoms, affects approximately 1% of the total population worldwide.[1] Although antipsychotics are effective in preventing relapse in patients with schizophrenia, approximately 24% of patients relapse within a year despite drug treatment.[2] Up to 30% of these patients have treatment-resistant schizophrenia (TRS), which is commonly defined as schizophrenia unresponsiveness to 2 or more courses of dopaminergic antipsychotic therapy, and clozapine is still considered to be the only effective pharmacotherapy for TRS.[3]

Patients with TRS have poorer outcomes in multiple functional domains. Because of persistent positive, negative, and cognitive symptoms, these patients have lower marriage rates, higher rates of residence in treatment facilities, and worsened social functioning than patients with other psychiatric disorders.[4,5] Schizophrenia relapse can lead to a risk of suicide, loss of productivity, and hospitalization and its attendant costs.[6] In a previous retrospective study, more than half of the

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patients with schizophrenia had relapsed once in 2 years, and four-fifths of them had relapsed more than once in 5 years.[7] Apart from psychopathological severity, the number of hospital admissions of a patient with schizophrenia was used to pragmatically define relapse in naturalistic settings in a previous systematic literature review.[8]

Clozapine is the only approved pharmacotherapy option for TRS. In a previous systemic review and meta-analysis, the response rate to clozapine among patients with TRS ranged from 25% to 60%, with the mean reduction in the Positive and Negative Syndrome Scale score being 25.8% from baseline.[9,10] From a pharmacologic perspective, the high efficacy of clozapine in treating patients with TRS may be related to its additional and complex affinity to receptors other than dopaminergic ones.[11] However, clozapine's side effect profile still raises clinical concerns, such as dose-related epilepsy and agranulocytosis, in addition to less severe adverse effects, such as sedation, weight gain, and constipation.[12] A previous network meta-analysis reported a relatively low risk ratio for all-cause clozapine discontinuation in comparison with other oral antipsychotics (OAPs).[13] However, 40%–70% of patients with TRS still exhibit a poor response to adequate clozapine monotherapy.[10]

For patients with TRS, further augmentation strategies, including antipsychotic polypharmacy with concomitant OAPs, add-on long-acting injectable (LAI) antipsychotics, or electroconvulsive therapy (ECT), have been discussed. A previous systemic review discussed the use of ECT in combination with clozapine; however, 14%–36% of the patients experienced adverse events.[14,15] Antipsychotic polypharmacy therapy with clozapine combined with various OAPs has also been discussed in studies. Multiple randomized controlled trials have compared different combination therapies; however, high-quality evidence regarding the superiority of any combination therapy is still lacking.[16] One randomized control trial determined that OAP polypharmacy was unnecessary after comparing the olanzapine-clozapine group with the clozapine monotherapy group.[17] Nevertheless, increasing numbers of studies are being conducted on combination therapy with clozapine and LAI antipsychotics for acutely ill patients with TRS. The use of LAI antipsychotics with clozapine is apparently well tolerated in these patients and may have beneficial effects over the course of the disease, including a shorter duration of hospitalization and a greater reduction in symptom severity.[18,19]

Significantly decreased quality of life and increased socioeconomic burden have been reported to result from symptoms relapse of TRS and psychiatric hospitalization.[20] Among patients taking clozapine, current evidence about relapse prevention by comparing combination with OAP or with LAI is scarce. One randomized controlled trial[21] and 1 open-label trial[22,23] supported that adding risperidone LAI before clozapine administration could lower psychosis severity. Three mirror-image studies[18,24,25] showed that, in the same patient group taking clozapine, LAI administration could lead to better clinical prognosis compared to the periods before LAI administration. However, direct comparison between the clozapine only, CLO + OAP, and CLO + LAI groups still needs to be addressed. Therefore, this study aims to analyze whether clozapine-LAI combination therapy was superior to clozapine-OAP combination therapy or to clozapine monotherapy in reducing the risk of psychiatric rehospitalization in acutely ill patients with TRS, with a 12-year cohort. Time to rehospitalization was the primary outcome measure, and covariates that could affect the outcome measure were adjusted.

METHODS

Subjects

This observational study with a retrospective cohort design was conducted at Taoyuan Psychiatry Center, a 957-bed public tertiary psychiatric center located in northern Taiwan. Patient data were retrospectively extracted through a review of charts and electronic medical records. The subjects were inpatients diagnosed with schizophrenia or schizoaffective disorder according to the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM*)*, Fourth Edition, Text Revision,* or *DSM, Fifth Edition*, criteria.[26,27] Patients who were acutely ill, admitted due to schizophrenia or schizoaffective disorder, and discharged on clozapine and concomitant OAPs or LAIs between January 1, 2006, and December 31, 2017, were included. Each patient was followed up for 365 days to assess whether they were readmitted during this period. The patients were divided into 3 groups, clozapine monotherapy (CLO), clozapine combined with any other oral antipsychotic medications (CLO + OAP), and clozapine combined with any LAI antipsychotic medications (CLO + LAI), according to the pharmacologic treatment modalities from medical records on the day of discharge.

In this study, treatment-resistant schizophrenia (TRS) was defined as the persistence of symptoms despite ≥2 trials of antipsychotic medications of adequate dose and duration with documented adherence according to the policy of the Taiwan Food and Drug Administration to administer clozapine. Diagnoses were made by board-certified psychiatrists and supported by clinical observations and interviews with the staff, information reported by primary caregivers, and past medical records of the patients. Patients with seizure disorder or physical illnesses that could potentially influence brain function were excluded.

The patients included in this study were categorized into 3 distinct groups based on their treatment regimens: clozapine monotherapy (CLO), combination therapy involving clozapine and any other OAPs (CLO + OAP), and combination therapy comprising clozapine and LAI antipsychotics, regardless of the presence or absence of additional OAPs (CLO + LAI). Additional details regarding OAPs and LAI antipsychotics received by the studied patients are presented in Supplementary Tables 1 and 2. This categorization facilitated the examination and comparison of outcomes associated with different treatment approaches, thus providing a comprehensive understanding of the effects of each therapeutic strategy on the risk of rehospitalization.

Covariates that could affect the time to rehospitalization, including age; sex; previous hospitalizations (times); daily clozapine dosage; need for compulsory hospitalization; and concomitant use of mood stabilizers (lithium, valproate, carbamazepine, or lamotrigine), antidepressants, benzodiazepines, anticholinergics, and laxatives, were adjusted using the Cox proportional hazards multivariate regression model. The backward elimination variable selection method was used to reduce variables for the final model with a conventional *P* value threshold of 0.10. Otherwise, the significance level for all statistical analyses was set at $P < .05$.

Follow-Up Procedures

Patients were followed up at the outpatient clinics of Taoyuan Psychiatry Center after discharge. Medications that were effective for acutely ill patients during hospitalization were continued after the patients were stabilized for a period, were discharged from the acute ward, and entered the maintenance phase of treatment. The frequency of outpatient visits ranged from weekly to biweekly, monthly, or trimonthly depending on clinician judgments and patient preferences. No other specialized nonmedication treatment was provided apart from routine education and counseling at the outpatient clinic.

The primary outcome of this study was time to rehospitalization within a year after discharge. The clinical indication for rehospitalization was the relapse or recurrence of significant psychiatric symptoms, dangerous or violent behaviors, or functional deterioration that responded inadequately to outpatient treatment. Patients with incomplete data of prescription on the discharge day were excluded from the analysis. For instance, patients who were transferred to another facility because of other medical conditions necessitating inpatient treatment or who participated in other clinical trials before or during the follow-up period were excluded.

Statistical Analyses

Statistical analyses were performed using R version 4.1.3 with the dplyr package. To analyze the demographic characteristics, the Pearson χ^2 test was used for categorical variables, and one-way analysis of variance (ANOVA) followed by the Scheffe post hoc test was used for continuous variables. The time to rehospitalization was assessed using Kaplan-Meier survival analysis, and between-group comparisons were performed using the log-rank test.

Two sensitivity analyses were performed to rule out the effect of previous or coexisting substance use and OAP use in the CLO + LAI group. In the first sensitivity analysis, patients with previous or concomitant illicit substance use (*International Classification of Diseases, Ninth* [*Tenth*] *Edition, Clinical Modification* [*ICD-9-CM*], code 304, 305, or 292 or *ICD-10-CM* code F11–16, F18, or F19) were excluded because of the significant impact of these substances on the outcome of schizophrenia.[28,29] Although coexisting alcohol or nicotine use disorder can also negatively impact the disease course of schizophrenia, clinicians did not regularly note the presence of alcohol or nicotine use disorder in medical records because alcohol and nicotine were not regulated under existing law in the practice background of Taiwan. In the second sensitivity analysis, 9 patients receiving clozapine, LAI antipsychotics, and other OAPs concomitantly were excluded to confirm that the protective effect in the CLO + LAI group was purely attributed to clozapine and concomitant LAI antipsychotics.

One subgroup analysis was also performed to bolster the study results. Because daily clozapine dosage and number of previous admissions are often linked with the severity and refractoriness of psychosis, these 2 variables could directly influence our main outcome of time to rehospitalization. These 2 covariates were thus adjusted by stratifying them into subgroups. Homogeneous subgroups were formed in order to manage selective bias and the possible effects of uncollected data, such as those concerning symptom severity.

Ethics

This study was approved by the Institutional Review Board of Taoyuan Psychiatry Center, Ministry of Health and Welfare, and was conducted in accordance with the Declaration of Helsinki (2013) and Taiwan's national legislation (Human Subjects Research Act, Taiwan). As this was a register-based study using anonymized data, informed consent was not required.

RESULTS

Demographic and Clinical Characteristics

A comparison of the baseline characteristics of the study participants is presented in Table 1. A total of 719 patients with schizophrenia or schizoaffective

Table 1.

Comparison of Baseline Clinical Characteristics Between Groups[a]

	Total	CLO	CLO + OAP	CLO + LAI	*P*
Age, y, mean ± SD	41.64 ± 11.86	42.01 ± 12.01	41.10 ± 11.65	39.82 ± 11.01	.349[b]
Clozapine dosage, mg, mean ± SD	306.87 ± 149.22	294.14 ± 136.26	358.97 ± 176.93	276.59 ± 146.96	**<.001**[b]
No. of previous admissions, mean ± SD	2.67 ± 3.36	2.42 ± 3.04	2.51 ± 2.95	5.51 ± 5.47	**.003**[b]
N (%) of total	719 (100%)	508 (70.7%)	156 (21.7%)	55 (7.6%)	
Male	360 (50.1%)	250 (49.2%)	79 (50.6%)	31 (56.3%)	.594[c]
Valproate	249 (34.6%)	164 (32.3%)	66 (42.3%)	19 (34.5%)	.071[c]
Lithium	36 (5.0%)	28 (5.5%)	6 (3.8%)	2 (3.6%)	.628[c]
Valproate + lithium	11 (1.5%)	8 (1.5%)	3 (1.9%)	0 (0.0%)	.600[c]
Carbamazepine	2 (0.3%)	1 (0.2%)	1 (0.6%)	0 (0.0%)	.602[c]
Lamotrigine	2 (0.3%)	1 (0.2%)	1 (0.6%)	0 (0.0%)	.602[c]
Antidepressant	104 (14.5%)	76 (15.0%)	24 (15.4%)	4 (7.3%)	.285[c]
Benzodiazepine	390 (54.2%)	256 (50.4%)	104 (66.7%)	30 (54.5%)	**.002**[c]
Anticholinergics	258 (35.9%)	155 (30.5%)	80 (51.3%)	23 (41.8%)	<.001
Laxatives	382 (53.1%)	260 (51.2%)	92 (59.0%)	30 (54.5%)	.228[c]
Involuntary admissions	3 (0.4%)	2 (0.4%)	0 (0.0%)	1 (1.8%)	.196[c]
ECT	16 (2.2%)	12 (2.4%)	3 (1.9%)	1 (1.8%)	.927[c]
Hypertension	124 (17.2%)	98 (19.3%)	17 (10.9%)	9 (16.36%)	.052[c]
Diabetes mellitus	31 (4.3%)	25 (4.9%)	3 (1.9%)	3 (5.5%)	.248[c]
Dyslipidemia	19 (2.6%)	12 (2.4%)	6 (3.9%)	1 (1.8%)	.555[c]
Gout	7 (1.0%)	4 (0.8%)	2 (1.3%)	1 (1.8%)	.690[c]
Hepatitis	2 (0.3%)	1 (0.2%)	0 (0.0%)	1 (1.8%)	.999[c]
Asthma	4 (0.6%)	4 (0.8%)	0 (0.0%)	0 (0.0%)	.434[c]
Rehospitalization in 3 mo	254 (35.3%)	182 (35.8%)	65 (41.2)	7 (12.7%)	**.001**[c]
Rehospitalization in 6 mo	299 (41.6%)	205 (40.4%)	77 (49.4%)	17 (30.9%)	**.034**[c]
Rehospitalization in 1 y	370 (51.5%)	264 (52.0%)	86 (55.1%)	20 (36.4%)	.052[c]

[a]Values shown as N (%) unless otherwise noted. Bold *P* values indicate a statistically significant difference. Physical diseases recorded equal to or less than once in this cohort are not presented.
[b]One-way ANOVA with Scheffe test.
[c]χ^2 test.
Abbreviations: ANOVA = analysis of variance, CLO = clozapine, ECT = electroconvulsive therapy, LAI = long-acting injectable antipsychotic, OAP = oral antipsychotic.

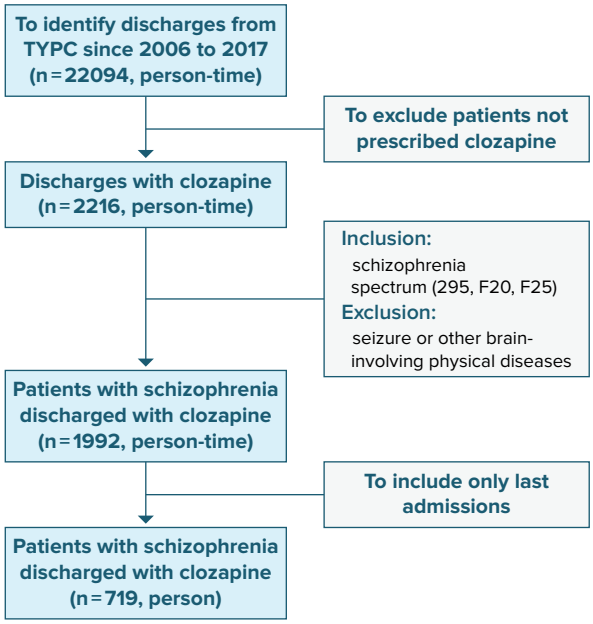
disorder who were discharged on clozapine during the study period were included in this study. A flow diagram of the recruited patients is shown in Figure 1. The gender of the patients was evenly distributed in all 3 treatment groups. Three patients had involuntary admissions. Of the patients discharged on clozapine, 508 (70.7%) received clozapine monotherapy (CLO group), 156 (21.7%) received concomitant OAPs (CLO + OAP group), and 55 (7.6%) received LAI antipsychotics (CLO + LAI group) at discharge. The mean age of the patients was 41.64 ± 11.86 years. ANOVA revealed that the daily clozapine dosage significantly differed among the 3 groups ($P < .001$). Subsequently, Scheffe post hoc test revealed that patients in the CLO + OAP group were prescribed significantly more clozapine than those in the CLO group ($P < .001$) and the CLO + LAI group ($P = .002$). Regarding the number of previous admissions, ANOVA and subsequent Scheffe post hoc test revealed that patients in the CLO + LAI group had significantly higher numbers of previous hospitalizations than did those in the other 2 groups ($P < .001$ and $P < .001$). The use of concomitant medications, including mood stabilizers (valproate, lithium, carbamazepine, or lamotrigine), antidepressants, benzodiazepines, and laxatives, was also analyzed. The use of benzodiazepines ($P = .002$) and anticholinergics ($P < .001$) significantly differed among the 3 groups, and the defined daily dose of anticholinergics was 0.21 ± 0.39, 0.37 ± 0.53, and 0.23 ± 0.38 in the CLO group, CLO + OAP group, and CLO + LAI group ($P < .001$), respectively. No other significant difference was noted in the proportion of concomitant medication users among the 3 groups.

Daily Dose of Administered Psychotropic Medications

The daily dose of prescribed concomitant psychotropic medications, including OAPs, LAIs, valproate, and lithium, was further assessed (Table 2). The dose of antipsychotics has been displayed with the chlorpromazine equivalent dose, according to previous international consensus.[30] In the CLO + LAI group, 9 of 55 patients received concomitant OAPs. The mean daily dose of the prescribed OAPs was 479.78 ± 317.42 and 844.44 ± 559.27 mg/d in the CLO + OAP and CLO + LAI

Figure 1.

Graphical Depiction of Study Design: Rehospitalization Within 365 d or Exceeding 365 d in Outpatient Follow-Up



Abbreviation: TYPC = Taoyuan Psychiatric Center.

groups, respectively. In all the patients, the mean dose of prescribed valproate was 932.93 ± 362.37 mg/d and that of prescribed lithium was 988.89 ± 284.63 mg/d. There was no significant difference in the use of prescribed mood stabilizers among the 3 groups (Table 2).

Rate of Rehospitalization Within a Year

The rate of rehospitalization within a year after index discharge from the acute inpatient psychiatric hospital was analyzed in the 3 groups. The cumulative rehospitalization rate of all the patients was 35.3%, 41.6%, and 51.5% within 3 months, 6 months, and 1 year after discharge, respectively. The rate of rehospitalization within 3 months ($P = .001$) and 6 months ($P = .034$) after discharge significantly differed among the 3 groups. The CLO + LAI group had a lower cumulative rehospitalization rate (36.4%) than the other 2 groups within a year after discharge; however, the difference was not significant ($P = .052$; Table 1). A survival curve of the 3 groups was obtained through Kaplan-Meier survival analysis (log-rank test, $P = .022$; Figure 2). The rehospitalization time of each group in months 3, 6 and 12 was listed as follows, respectively (days, mean ± SD): CLO group: 67.49 ± 35.24, 123.75 ± 76.07, and 220.99 ± 157.78; CLO + OAP group: 63.03 ± 36.05, 112.14 ± 77.79, and 199.47 ± 162.56; and CLO + LAI group: 86.67 ± 14.28, 157.25 ± 44.99, and 277.98 ± 124.15.

Hazard Ratio for Rehospitalization

The hazard ratio (HR) for rehospitalization was assessed using Cox regression analysis (Table 3). The included variables are mentioned in "Methods." The CLO group and the CLO + OAP group had significantly higher HRs (HRs, 2.50 and 2.69, respectively) than the CLO + LAI group. The backward elimination method with a threshold of 0.1 was adopted in the Cox regression. After the stepwise elimination, the other variables in the Cox regression model were age, daily clozapine dosage, number of previous admissions, and sex.

As shown in Supplementary Table 5, each subgroup stratified by the daily clozapine dosage and number of previous admissions was further analyzed. Despite the HR in the CLO + OAP group being comparable to that of the CLO + LAI group for patients having 6 or more previous admissions [2.25 (0.95–5.33)], the HRs of the remaining subgroups were significantly higher than that of the CLO + OAP group (Table 3).

Sensitivity Analyses

In the first sensitivity analysis performed according to the *ICD-9-CM* and *ICD-10-CM* criteria, patients having substance-related minor diagnoses (diagnostic codes listed under "Methods") were filtered out. Ten patients were excluded, and the remaining 709 patients were retained for subsequent sensitivity analysis. The results and variables remaining in the equation did not differ from those in the main analysis of HRs [CLO vs CLO + LAI: HR, 2.35, 95% CI, 1.46–3.77; CLO + OAP vs CLO + LAI: HR, 2.54, 95% CI, 1.53–4.22].

Nine patients who concomitantly received clozapine, OAPs, and LAI antipsychotics were excluded from the second sensitivity analysis (CLO vs CLO + LAI: HR, 2.53, 95% CI, 1.52–4.22; CLO + OAP vs CLO + LAI: HR, 2.72, 95% CI, 1.58–4.70). The results and variables remaining in the equation were still similar to those in the main analysis of HRs.

DISCUSSION

In the current study, the combination of clozapine and LAI antipsychotics emerged as a significant factor associated with a substantially reduced risk of rehospitalization among the studied patients. Comparatively, both the combination of clozapine and OAPs and clozapine monotherapy exhibited a higher risk of rehospitalization. These findings shed light on the potential advantages of incorporating LAI antipsychotics into the treatment regimen alongside clozapine.

Based on the demographic and clinical characteristics listed in Table 1, the gender of patients receiving pharmacotherapy with clozapine was evenly distributed. Moreover, clozapine monotherapy was the prevalent treatment option in the psychiatric center in

Table 2.

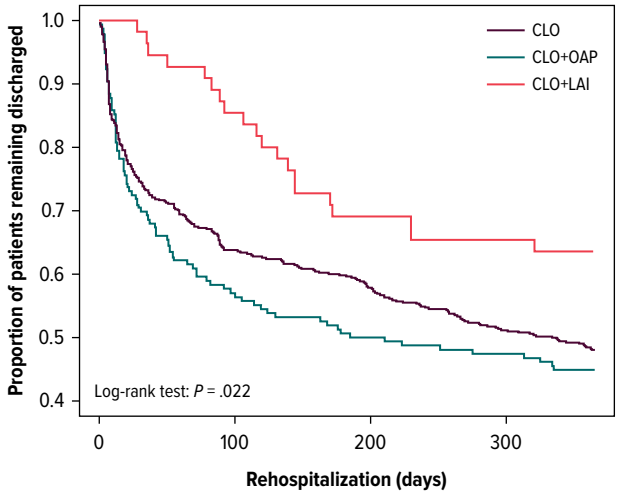
Daily Dose (mg/d) of Each Administered Psychotropic[a]

	Total	CLO	CLO + OAP	CLO + LAI	*P*
OAP			479.78 ± 317.42	844.44 ± 559.27	
LAI				462.96 ± 259.89	
Valproate	932.93 ± 362.37	900.61 ± 336.57	1013.64 ± 418.01	931.58 ± 344.89	.101[b]
Lithium	988.89 ± 284.63	996.43 ± 280.84	933.33 ± 355.90	1050.00 ± 212.13	.851[b]

[a]Only patients prescribed the corresponding medications were included. Nine of 55 patients in the CLO + LAI group also received OAPs. The dose of antipsychotics has been displayed with the chlorpromazine equivalent dose.
[b]One-way ANOVA.
Abbreviations: ANOVA = analysis of variance, CLO = clozapine, LAI = long-acting injectable antipsychotic, OAP = oral antipsychotic.

Figure 2.

Survival Curve of the Studied Groups[a]



[a]The data were obtained through Kaplan–Meier survival analysis.
Abbreviations: CLO = clozapine, LAI = long-acting injectable antipsychotic, OAP = oral antipsychotic.

Table 3.

Hazard Ratio (HR) for Rehospitalization in a Year[a]

	HR	95% CI of HR	*P* value
CLO vs CLO + LAI group	2.50	1.56–4.01	**<.001**
CLO + OAP vs CLO + LAI group	2.69	1.62–4.46	**<.001**
Age	1.02	1.01–1.03	**<.001**
CLO daily dosage	1.00	1.00–1.00	**.002**
Numbers of previous admissions	1.10	1.08–1.12	**<.001**
Sex[b]	1.23	0.99–1.51	.051

[a]The data were obtained using Cox regression analysis. Adjusted covariates: age; sex; previous hospitalizations (times); daily clozapine dosage; compulsory hospitalization; and concomitant use of mood stabilizers (lithium, valproate, carbamazepine, or lamotrigine), antidepressants, benzodiazepines, anticholinergics, and laxatives. Bold *P* values indicate a statistically significant difference.
[b]The reference was set at female gender.
Abbreviations: CLO = clozapine, LAI = long-acting injectable antipsychotic, OAP = oral antipsychotic.

northern Taiwan. Among the patients treated with clozapine monotherapy, up to 40% received mood stabilizers, mainly valproate, concomitantly. Similarly, approximately 40% of the patients in the other 2 groups received valproate concomitantly. According to the published consensus guidelines on the definition of TRS and augmentation strategies for patients with schizophrenia receiving clozapine from the Treatment Response and Resistance in Psychosis working group, one of the recommendations in the case of poor treatment response to clozapine monotherapy was to achieve a therapeutic serum clozapine level of 350–450 ng/mL. Furthermore, consensus was reached on combinations with aripiprazole or amisulpride as the second antipsychotic, augmentation with ECT, and the use of antidepressants or mood stabilizers in various clinical scenarios.[31,32] Although evidence suggests that aripiprazole and amisulpride might be superior to other antipsychotics when augmenting clozapine, only a small proportion (n = 9/156) of patients in the CLO + OAP group received aripiprazole (n = 4) or amisulpride (n = 5). Notably, no patients in the CLO + LAI group received a LAI formulation of aripiprazole. The use of sodium valproate as an augmentative treatment strategy with clozapine for TRS has been proposed in multiple previous studies.[33,34] Improved therapeutic effectiveness and reduced incidence of epilepsy have been reported in patients receiving such treatment.[35,36] However, additional risk of adverse events, such as neutropenia and myocarditis, following the concomitant administration of clozapine and valproate has also been reported in previous studies.[37–39]

Due to the particularities of their disease, the patients in the CLO + OAP group may have been more refractory to clozapine monotherapy. The prescribed daily dose of valproate was higher in the CLO + OAP group than in the

CLO group, although the difference was not significant (Table 2). Our results revealed that patients receiving antipsychotic polypharmacy therapy were more likely to be prescribed a higher dose of valproate comedication. Antipsychotic polypharmacy has been reported to be a proxy measure of increased disease acuity, severity, complexity, and chronicity.[40] In particular, the patients in the CLO + OAP group may have had more severe and refractory disease compared with those in the CLO group; therefore, clinicians may have tended to use polypharmacy strategies on the basis of the current evidence regarding the augmenting effect of valproate.

Regardless of the type of LAI antipsychotic, these drugs have been reported to reduce the odds of nonadherence and lower the rates of rehospitalization, with the total health care costs being consistent over 6 months.[41,42] Comparative studies on the effectiveness of antipsychotic drugs in reducing the rates of rehospitalization in patients with schizophrenia have revealed that clozapine and LAI antipsychotics are among the best treatment options for adults with first-episode psychosis or those aged over 60 years.[43,44] However, to the best of our knowledge, the effectiveness of LAI antipsychotics in preventing rehospitalization in patients with schizophrenia who are being treated with clozapine, a second-line choice of antipsychotic that is primarily used for patients with TRS, has not been discussed in detail previously.

The protective effect of LAI antipsychotics in patients with refractory schizophrenia treated with clozapine in a natural environment was observed in this study. Table 2 presents a comparison of the rates of rehospitalization among the 3 groups within 3 months, 6 months, and 1 year after previous discharge. Significant advantages of clozapine-LAI combination therapy were noted at the 3-month ($P = .001$) and 6-month ($P = .034$) time points; these protective effects further extended to the 12-month ($P = .052$) time point. This result may reach statistical significance with a larger sample size. Most patients with schizophrenia spectrum disorder experience relapses, and their nonadherence to pharmacotherapy is one of the main contributors to relapse.[45,46] To prevent relapse, the benefits of early use of LAI antipsychotics as a first-line treatment strategy during the first episode of psychosis have been emphasized in recent studies.[47,48] The results of our retrospective cohort study support the benefits of LAIs in patients with TRS spectrum disorder.

Significant reductions in the HRs for rehospitalization were noted in the CLO + LAI group when compared with the other 2 groups and even when compared between subgroups stratified by daily clozapine dosage and number of previous admissions. The protective effects may be greater in patients with fewer than 2 previous admissions than in those with more than 3 previous admissions; however, we did not perform a formal analysis to verify this. The evidence of neurodegeneration and its relationship with recurrent psychotic episodes—based on data obtained through functional brain imaging—in a previous study indicated that the degree of brain region dysfunction was positively correlated with the number of relapses.[49] A relapse of schizophrenia spectrum disorder poses the biological risk that a patient may not return to their previous level of function after a period of active psychosis. This is associated with impaired treatment outcomes.[50] Our results indicated that LAI comedication may lead to better outcomes even in patients with TRS being treated with clozapine.

There are a few limitations to consider in this study. First, while we included several clinical and demographic variables, data on other factors such as symptom severity, functional impairment, comorbidities, and medication side effects were not available. While all patients continued treatment at Taoyuan Psychiatric Center postdischarge, our analysis lacked outpatient prescription data, limiting our ability to consider potential changes in treatment regimens or variations in other outpatient interventions that could impact time to rehospitalization (eg, partial hospitalization, group therapy, and social interventions). These unmeasured variables may have affected the results of the study but were not accounted for in the analysis. However, we did adjust for variables related to symptom severity and disease course refractoriness (eg, daily clozapine dosage and number of previous admissions). Second, using time to rehospitalization as an indicator of poor treatment outcomes may not be applicable in all clinical situations. Third, this study was conducted at a single hospital and only included patients who received inpatient treatment at this hospital, which may limit the generalizability of our findings. Fourth, due to the absence of an anesthesiologist in our psychiatric center, only a small number of patients included in this study received ECT (n = 16) during their hospitalization, despite its recognized efficacy in TRS. Moreover, we encountered difficulties in retrieving information regarding whether the patients underwent ECT treatment at another medical center prior to or during the study period. Fifth, the serum clozapine levels, which were suggested to be monitored to evaluate treatment adherence and whether they reached the therapeutic range in previous studies, were unable to be retrieved in this retrospective cohort study. Sixth, the heterogeneity in the mechanisms of OAPs administered in the studied cohort was not effectively addressed in this study; instead, they were grouped together. Finally, the rate of comorbidity between schizophrenia and substance use may be underestimated in this cohort.

In this study, the combination of clozapine and LAI antipsychotics was associated with a significantly lower risk of rehospitalization compared to both the combination of clozapine and OAPs and clozapine

monotherapy. Even when subgrouped by daily clozapine dosage or number of previous hospitalizations, the result remained the same. The clinical implication of our findings is that the use of LAI antipsychotics should be considered to prevent rehospitalization in patients treated with clozapine who have a clinically refractory disease course. Further studies focusing on other preventive interventions against rehospitalization and on the long-term effectiveness of clozapine-LAI combination therapy in preventing rehospitalization should be conducted in the future.

Article Information

Published Online: May 1, 2024. https://doi.org/10.4088/JCP.23m15071

Submitted: August 24, 2023; accepted December 29, 2023.

To Cite: Tien Y, Wang X-Y, Huang S-C, et al. Beneficial effects of concomitant long-acting injectable antipsychotics on time to rehospitalization in patients with treatment-resistant schizophrenia receiving clozapine: a retrospective cohort study. *J Clin Psychiatry*. 2024;85(2):23m15071.

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Relevant Financial Relationships: None.

Funding/Support: None.

Supplementary Material: Available at Psychiatrist.com.

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The Journal of Clinical Psychiatry

Supplementary Material

Article Title: Beneficial Effects of Concomitant Long-Acting Injectable Antipsychotics on Time to Rehospitalization in Patients With Treatment-Resistant Schizophrenia Receiving Clozapine: A Retrospective Cohort Study

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DOI Number: 10.4088/JCP.23m15071

LIST OF SUPPLEMENTARY MATERIAL FOR THE ARTICLE

DISCLAIMER

Supplementary Table 1 Number of patients using each LAI.

	CLO+LAI(n=55)
Clopenthixol	5
Flupentixol	3
Fluphenazine	28
Haloperidol	16
Risperidone	3

Supplementary Table 2 Number of patients using different oral antipsychotic combinations, among the CLO+OAP and CLO+LAI groups

	CLO+OAP (n=156)	CLO+LAI (n=55)
None	0	46
Amisulpride	5	0
Aripiprazole	4	0
Chlorpromazine	6	0
Chlorpromazine+Risperidone	1	0
Clotiapine	3	0
Clotiapine+Olanzapine	1	0
Flupentixol	3	0
Haloperidol	32	3
Loxapine	1	0
Olanzapine	8	0
Olanzapine+Risperidone	1	0
Paliperidone	1	0
Risperidone	12	2
Sulpiride	70	3
Sulpiride+Olanzapine	1	0
Sulpiride+Risperidone	1	0
Trifluoperazine	2	0
Ziprasidone	1	0
Zotepine	2	1
Zuclopenthixol	1	0

Supplementary Table 3 Cox regression of hazard ratio for rehospitalization in a year (Full model)

	Full model		Final model	
	HR (CI)	**p**	**HR (CI)**	**p**
CLO vs. CLO+LAI	2.53 (1.57-4.07)	**<.001**	2.50 (1.56-4.01)	**<.001**
CLO+OAP vs. CLO+LAI	2.66 (1.60-4.42)	**<.001**	2.69 (1.62-4.46)	**<.001**
CLO+OAP vs. CLO	1.05 (0.82-1.36)	.697	1.08 (0.84-1.38)	.569
Age	1.02 (1.01-1.03)	**<.001**	1.02 (1.01-1.03)	**<.001**
Clozapine daily dosage	1.00 (1.00-1.00)	**.025**	1.00 (1.00-1.00)	**.002**
Previous admissions	1.10 (1.08-1.12)	**<.001**	1.10 (1.08-1.12)	**<.001**
Sex	1.24 (1.01-1.53)	**.044**	1.23 (0.99-1.51)	.051
Involuntary admission	0.91 (0.45-1.84)	.795	-	-
Lithium	1.22 (0.77-1.93)	.390	-	-
Valproate	1.08 (0.87-1.34)	.473	-	-
Carbamazepine	1.65(0.23-12.03)	.624	-	-
Lamotrigine	0.92 (0.12-6.75)	.931	-	-
Antidepressant	1.09 (0.80-1.47)	.601	-	-
Benzodiazepine	0.92 (0.75-1.15)	.470	-	-
Anticholinergics	1.14 (0.92-1.43)	.238	-	-
Laxatives	1.11 (0.90-1.37)	.341	-	-

HR (CI): hazard ratio (95% confidence interval).
Full model: prior to backward stepwise elimination.
Final model: after backward stepwise elimination.
Bold p-values indicate a statistically significant difference.
Continuous variables: age, clozapine daily dosage, number of previous admissions
Categorical variables: sex (reference set at female), compulsory hospitalization; and concomitant use of mood stabilizers (lithium, valproate, carbamazepine, or lamotrigine), antidepressants, benzodiazepines, anticholinergics, and laxatives.

Supplementary Table 4 Cox regression of hazard ratio for rehospitalization in a year of the first hospitalization (Full model)

	Full model	
	HR (CI)	**p**
CLO vs. CLO+LAI	2.39 (1.57-3.64)	**<.001**
CLO+OAP vs. CLO+LAI	2.51 (1.59-3.98)	**<.001**
Age	1.01 (1.01-1.02)	.092
Clozapine daily dosage	1.00 (1.00-1.00)	**.001**
Previous admissions	1.11 (1.09-1.13)	**<.001**
Sex	1.27 (1.05-1.53)	**.014**
Involuntary admission	0.74 (0.18-3.00)	.670
Lithium	1.34 (0.92-1.94)	.127
Valproate	1.21 (0.99-1.48)	.058
Carbamazepine	2.59(0.15-20.37)	.989
Lamotrigine	0.98 (0.31-3.09)	.973
Antidepressant	1.29 (0.99-1.67)	**.046**
Benzodiazepine	0.92 (0.76-1.11)	.394
Anticholinergics	1.07 (0.88-1.30)	.515
Laxatives	1.05 (0.87-1.28)	.592

Supplementary Table 5 Hazard ratio for rehospitalization in each selected subgroup

	CLO (*n* = 508)		**CLO+OAP (*n* = 156)**		**CLO+LAI (*n* = 55)**	
	N	**HR (95% CI)**	**N**	**HR (95% CI)**	**N**	**HR (95% CI)**
	508	**2.50 (1.56-4.01)**	156	**2.69 (1.62-4.46)**	55	1
Grouped by daily clozapine dosage						
≦200 mg	168	**2.98 (1.41-6.30)**	43	**2.86 (1.21-6.74)**	24	1
201-399 mg	198	**2.59 (1.00-6.72)**	34	**2.98 (1.07-8.28)**	14	1
≧400 mg	142	**2.94 (1.23-7.06)**	79	**3.04 (1.27-7.31)**	17	1
Grouped by numbers of previous admission						
0-2	341	**4.77 (1.18-19.28)**	98	**4.32 (1.04-17.95)**	17	1
3-5	108	**2.20 (1.10-4.41)**	37	**3.33 (1.57-7.06)**	19	1
≧6	59	**2.27 (1.06-4.87)**	21	2.25 (0.95-5.33)	19	1

The reference was set at the CLO + LAI group.

Bold values indicate a statistically significant difference.

Adjusted covariates: age; sex; previous hospitalizations (in daily clozapine dosage subgroups); daily clozapine dosage (in number of previous admission subgroups); compulsory hospitalization; and concomitant use of mood stabilizers (lithium, valproate, carbamazepine, or lamotrigine), antidepressants, benzodiazepines, anticholinergics, and laxatives.