Citation: Clin Transl Sci (2020) 13, 1170–1177; doi:10.1111/cts.12801

ARTICLE

Persistence of Antipsychotic Use After Clozapine Discontinuation: A Real-World Study Across Antipsychotics

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Although clozapine treatment is often discontinued due to limited efficacy or low tolerability, there is a lack of guidelines and evidence on treatment options after discontinuation of clozapine in patients with schizophrenia. Persistence has proven to be an adequate indicator for treatment effectiveness in patients with schizophrenia. The aim of this study was, therefore, to compare persistence of antipsychotic use between antipsychotic treatment options in patients after stopping clozapine treatment. Registry data from a prescription database representative of the Dutch population (1996–2017) was collected to investigate persistence in patients with schizophrenia who had been using clozapine for ≥ 90 days. Persistence with antipsychotics after clozapine discontinuation was analyzed using Cox-proportional hazard regression models. Our study population consisted of 321 participants, of whom 138 re-initiated clozapine and 183 started some other antipsychotic in the year after clozapine discontinuation (*N* = 518 antipsychotic use periods, *N* = 9,178 months). Second-generation antipsychotics (SGAs) as a group were associated with better persistence compared to first-generation antipsychotics (adjusted hazard ratio (aHR), 0.73; 95% confidence interval (CI) 0.57–0.93; *P* = 0.011). Compared with other antipsychotics, the following oral monotherapy antipsychotics were associated with significantly better persistence: restarting clozapine (aHR 0.48; 95% CI 0.32–0.71; *P* < 0.001) and switching to risperidone (aHR 0.52; 95% CI 0.32–0.84; *P* = 0.008) or olanzapine (aHR 0.55; 95% CI 0.35–0.87; *P* = 0.010). Sensitivity analyses confirmed the results. In conclusion, oral SGAs are associated with better persistence than alternative antipsychotic treatment options in patients discontinuing clozapine for undefined reasons. Especially clozapine (except in those with previous serious adverse reactions to clozapine), olanzapine and risperidone should be considered as oral monotherapy for these patients.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?
☑ Clozapine treatment is the treatment of choice in patients with therapy-resistant schizophrenia (TRS). Although clozapine discontinuation is frequently observed, there is a lack of guidelines and evidence on treatment options after clozapine treatment discontinuation in patients with schizophrenia.

WHAT QUESTION DID THIS STUDY ADDRESS?
☑ The aim of this study was to compare persistence of antipsychotic use between antipsychotic treatment options in patients stopping clozapine, with persistence being a proxy for efficacy.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?
☑ Second-generation oral antipsychotics (SGAs)—especially clozapine, olanzapine, and risperidone—are associated with better persistence than other antipsychotic treatment options in patients discontinuing clozapine for undefined reasons.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?
☑ Clinicians should consider oral monotherapy with SGAs, particularly clozapine (except in those with previous serious adverse reactions to clozapine), olanzapine, and risperidone for subjects who discontinued clozapine. Researchers designing randomized clinical trials for patients with TRS may consider our findings to prioritize the compounds to be investigated.

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Received: February 13, 2020; accepted: April 7, 2020. doi:10.1111/cts.12801

Schizophrenia is a severe psychiatric disorder, characterized by positive symptoms and negative symptoms. Positive symptoms include hallucinations, delusions, as well as disorganized speech and behavior. Negative symptoms include anhedonia, social withdrawal, lack of energy, and cognitive decline.[1–4] The lifetime incidence of the disease is ~ 0.7%.[3,4] It is estimated that there are around 120,000 patients with schizophrenia in The Netherlands.[5]

Multiple studies have shown the superior efficacy of clozapine over other antipsychotics, especially in reducing positive symptoms.[6–10] According to several national guidelines, clozapine is the only registered treatment option available for treatment-resistant schizophrenia (TRS).[7,11–13] TRS is generally defined as "failure to respond to two or more antipsychotics (one of which should be a second-generation antipsychotic, SGA), when given in an adequate dose for at least 6–8 weeks.[12,14,15] Around 30% of patients with schizophrenia are eventually considered TRS.[13,16] Of the patients with TRS who start clozapine therapy, ~ 50% discontinue clozapine therapy due to lack of effect or adverse events.[11,17–20] To date, no predictors for clozapine response have been identified.[21]

In patients with TRS who do not respond adequately to clozapine, three treatment strategies can be tried: augmenting with nonantipsychotic compounds, combining antipsychotics, and switching between antipsychotics.[22] A recent meta-analysis on clozapine combination and augmentation strategies in patients with TRS concluded that there are a few low-quality studies investigating these strategies, but there is a scarcity of high-quality studies. Little benefit was found for pharmacological augmentation (i.e., addition of a nonantipsychotic compound) and combination strategies (i.e., addition of an antipsychotic compound) when only high-quality studies with sufficient numbers of participants were included.[22] Furthermore, no randomized clinical trials (RCTs) on treatment options in patients who discontinue clozapine therapy have been published. Due to the lack of studies on these strategies, current guidelines do not provide a clear answer as to which of those treatment options is preferred in patients who discontinue their treatment with clozapine.[12,13] However, a recent Finnish registry study showed that re-initiation of clozapine and switching to oral olanzapine was associated with a lower risk of psychiatric rehospitalization, treatment failure, and mortality compared with switching to other antipsychotics in patients discontinuing clozapine.[23] Because those results are based on a single cohort in one country using those outcome measures, we reasoned it is worthwhile to evaluate if these antipsychotics are also preferred when looking at other outcome measures and in other countries, such as persistence of use in The Netherlands.

Persistence, defined as the time from initiation to all-cause discontinuation of therapy, has proven to be an adequate indicator for treatment efficacy, safety, and tolerability in patients with schizophrenia from patients' as well as clinicians' perspectives.[24–26] Long-term treatment with antipsychotics is associated with lower mortality compared with no use.[27] Moreover, multiple trials show that better persistence is associated with lower healthcare costs.[28,29] Low adherence, limited efficacy, and side effects are all causes of nonpersistence.[26] Nonadherence is a major issue in the treatment of patients with schizophrenia as it is associated with (re) hospitalization, suicide, delayed remission, poor prognosis, unemployment, and poor quality of life.[30]

A powerful approach to investigate drug persistence is a pharmacy drug dispensing study. In this study, we used the Dutch IADB.nl database that contains dispensing data from community pharmacies and is representative of the entire Dutch population (N = 17M[31]).[32–34] The data drawn from such a registry are more likely to reflect medication use in a real-world setting compared with data derived from RCTs as patients who enroll in RCTs may be more motivated to adhere to treatment, experience overall less severe symptoms, and have less comorbidities than patients in a real-world setting.[35] Pharmacy databases are particularly suited for the evaluation of medication intended for long-term use, such as antipsychotics.[36] Using this registry, we identified a large study population of patients who used clozapine (N = 2,627) to investigate the comparative persistence of pharmacological treatment options, including clozapine restart after clozapine treatment discontinuation. We hypothesized that SGAs are associated with better persistence than first-generation antipsychotics (FGAs) because of recent evidence pointing to their relatively better efficacy.[37,38] We also reasoned there would be no difference in persistence between antipsychotic monotherapy and polypharmacy after clozapine discontinuation as, on the one hand, polypharmacy may reduce symptoms more powerfully owing to better receptor occupancy, but, on the other hand, polypharmacy may incur more side effects.

MATERIALS AND METHODS

Data sources

Data was obtained from the University of Groningen IADB.nl. The authors were granted access to the database after submitting a research protocol for this study. This growing pharmacy prescription database contains prescription data from 1996 until 2017 from ~ 60 community pharmacies and covers an estimated population of 600,000 patients. Registration in the database is irrespective of healthcare insurance and age or sex. Prescription rates among the database population are representative of the Netherlands as a whole, and the database has been extensively used for research. Each patient has a unique anonymous identifier; date of birth and sex are known. Patients can be tracked with this anonymous identifier throughout the database period. Prescription records contain information on the date of dispensing, the quantity dispensed, the dose regimen, the number of days the prescription is valid, the prescribing physician, and the Anatomical Therapeutic Chemical (ATC) code. These variables provide information on a patient's drug-utilization patterns and can be used to investigate persistence. The medication records for each patient are virtually complete, due to the high patient-pharmacy commitment in the Netherlands, except for over-the-counter drugs and medication dispensed during hospitalization.[39] No ethics approval was required for this retrospective study, in accordance with the Dutch Guidelines for file research.

Study population

The study population consisted of former clozapine users, aged ≥ 18 years. Clozapine users were identified with ATC

code N05AH02. Patients who had used clozapine persistently for at least 3 months before discontinuing, were included in the study. Clozapine use was defined as use for at least 3 months to exclude patients who discontinued therapy too rapidly to evaluate effectiveness, as the therapeutic effect can only be assessed after several weeks of continuous use.[5] In the treatment groups, we differentiated between those restarting clozapine and those starting a different compound after clozapine discontinuation. Clozapine restarting patients had to restart clozapine in the period from 3 months until 1 year after clozapine discontinuation. This 3-month clozapine-free period was included to ensure that clozapine had been discontinued and the gap in dispensing dates was not due to noncompliance. The other group of participants, those starting a different antipsychotic after clozapine discontinuation, started using another antipsychotic in the year after clozapine discontinuation. These patients were not allowed to restart clozapine in that year. Only medication switches from clozapine to another antipsychotic occurring in the first year after clozapine discontinuation were examined to ensure that most time-related patient factors remained relatively stable. For example, if a patient discontinues clozapine, uses another antipsychotic for 2 months, and then restarts clozapine after 5 months, only the clozapine restart use period is included in the analysis. If a patient discontinues clozapine and switches to another compound after 1 month, discontinues that therapy, and switches to another antipsychotic within 1 year after discontinuing clozapine, both use periods are included in the analysis. To increase homogeneity of our study population with psychotic illness, patients with concomitant use of lithium were excluded (ATC N05AN01), as they possibly had bipolar disorder. Subjects with concomitant use of dopaminergic medication for Parkinson's disease (ATC N04B, excluding cabergoline) were also excluded because clozapine can be used to treat psychoses in Parkinson's disease. Patients with anticholinergic medication were not excluded, as these agents may also be used to treat extrapyramidal symptoms caused by antipsychotic medication.

Antipsychotic medication use that was initiated in the year after clozapine discontinuation was examined. Polypharmacy was defined as use of two or more antipsychotics for at least 30 days. This time factor was included to make a distinction between polypharmacy and cross-tapering. A distinction between oral and long-acting injectable (LAI) antipsychotics was made using Z-index numbers.

Outcome measures

The medication use periods were calculated by dividing the number of units delivered by the prescribed daily dose.[36] When the inserted daily dose was negative or zero for oral and LAI antipsychotics or ≥ 1 for an LAI antipsychotic, which was observed during data cleaning, persistence was based on the time between two dispensing dates and the number of units delivered, provided that the time between dispensing dates did not exceed the recommended dose interval. Persistence was defined as the period (in days) from initiation to discontinuation of dispensing, as we lacked clozapine blood levels to examine adherence otherwise.[40] Follow-up started at initiation of antipsychotic therapy in the year after clozapine cessation and ended at discontinuation or end of data linkage. When an antipsychotic was already started during clozapine treatment, the end date of clozapine therapy was set as the starting date of the other antipsychotic compound. Patients were considered persistent until a permissible gap of 30 days between two consecutive use periods was exceeded. The permissible gap was expanded to 90 days in our sensitivity analysis.

Data analyses

The Student's *t*-test was used to compare the number of men and women in the study population at baseline, whereas the Mann-Whitney *U* test was used to compare the age at discontinuation of clozapine and the duration of clozapine use between men and women. Persistence was analyzed using Cox proportional hazard regression models and survival curves were created to visualize potential differences, but instead of death the survival curves plot nonpersistence. The main analysis focused on the difference in persistence between monotherapy with FGAs and SGAs in patients who discontinued clozapine, with the FGAs as the reference group. The compounds (oral and/or LAI) included in the FGA-group were haloperidol, zuclopenthixol, flupentixol, levomepromazine, fluphenazine, pimozide, pipamperone, bromperidol, penfluridol, periciazine, tiapride, and thioridazine. The compounds (oral and/or LAI) included in the SGA group were clozapine, olanzapine, quetiapine, risperidone, aripiprazole, paliperidone, sulpiride, lurasidone, and sertindole. We performed two secondary analyses. The first secondary analysis was to compare the persistence between monotherapy and polypharmacy. These two analyses (main and first secondary) did not include clozapine restarters to determine what treatment options are most effective in patients for whom restarting clozapine is not an option. Covariates included in the main analysis and in the first secondary analysis were sex, age, type of antipsychotic (i.e., FGA or SGA), route of administration (i.e., oral or LAI), and type of therapy (i.e., monotherapy or polypharmacy).[41,42] Results are presented as adjusted hazard ratios (aHRs). The second secondary analysis was to determine what antipsychotic agent used as monotherapy or whether polypharmacy as a group was associated with the best persistence, including restarting clozapine. Oral and LAI antipsychotics were considered separately in this final analysis (e.g., olanzapine oral and olanzapine LAI were considered different antipsychotic agents). In addition, all agents with greater than five use periods available were included as individual monotherapy compounds, whereas all other antipsychotics given as monotherapy were considered one category (named "other antipsychotics") due to scarce numbers of observations per compound. This group of "other antipsychotics" was used as a reference group in this analysis. Covariates in the second secondary analysis were age and sex. The antipsychotics included as individual compounds were haloperidol, flupentixol, zuclopenthixol, zuclopenthixol LAI, olanzapine, quetiapine, sulpiride, risperidone, aripiprazole, paliperidone LAI, and polypharmacy. The compounds considered together in the "other antipsychotics" group (the

reference group) because they had less than five use period observations were levomepromazine, pipamperone, pimozide, periciazine, thioridazine, bromperidol, sertindole, penfluridol, tiapride, paliperidone, lurasidone, fluphenazine LAI, haloperidol LAI, flupentixol LAI, bromperidol LAI, olanzapine LAI, and risperidone LAI. The results for the individual compounds are also presented as aHRs.

Two additional analyses were performed. The first additional analysis included only the first initiated therapy after the first clozapine discontinuation, including each patient once. The second additional analysis investigated if the time between clozapine discontinuation and clozapine re-initiation influences persistence. Clozapine monotherapy restarters were divided into 2 groups: clozapine monotherapy restart within 4–8 months and within 9–12 months after discontinuation. Persistence with clozapine restart was compared between the two groups using the Mann–Whitney *U* test.

All statistical analyses were performed using IBM SPSS Statistics for Windows version 25.0 2017 (IBM, Armonk, NY). The level of statistical significance was set at $P < 0.05$.

RESULTS

In total, 2,627 patients who received a prescription for clozapine were identified in the database. Of these, 30% ($N = 779$) received medication for Parkinson's disease and were excluded. There were 1,344 patients who used clozapine for at least 90 days. Of these patients, 183 switched to another antipsychotic drug, whereas 138 patients re-initiated clozapine in the year after clozapine discontinuation (**Table 1**). Thus, a total of 321 patients were included in the analysis ($N = 518$ medication use periods and 454 switches; i.e., from clozapine to another antipsychotic, to polypharmacy, or back to clozapine). There were more use periods than switches, mostly due to polytherapy (as one switch from clozapine use to polytherapy results in more than one use period). A flow-chart of the process of inclusion and exclusion is shown in **Figure S1**. Mean follow-up time was 17.7 months (SD 27.6 months) and the total number of observed months for persistence was 9,178 months. Patients included in the study were more likely to be men (60.4%) than women ($P < 0.001$), with an average age of almost 43 years, logically resulting in more analyzed use periods of male participants and more switches made by male participants. Female patients were significantly older at the time of clozapine discontinuation than male patients ($P < 0.001$).

Of all antipsychotic agents prescribed as monotherapy after clozapine discontinuation, the most commonly prescribed were clozapine (21.8% of the switches), followed by oral olanzapine (10.3%), quetiapine (9.2%), oral risperidone

Table 1 Baseline characteristics of the study population

Characteristics	Entire cohort	Male participants	Female participants	*P* value (Student *t*-test for absolute number comparisons and Mann–Whitney *U* test for age comparisons)
Number of patients who met the inclusion criteria	321	194	127	< 0.001
Average age at discontinuation of clozapine, years (SD)	43.0 (14.0)	39.7 (11.9)	48.0 (15.6)	< 0.001
Number of use periods analyzed	518	314	204	< 0.001
Number of switches made	445	263	182	< 0.001
Most frequently initiated monotherapy and polypharmacy antipsychotics after clozapine discontinuation (oral unless otherwise stated)			Percentage of patients (*N*)	
Clozapine			21.8% (97)	
Polypharmacy without clozapine			15.1% (67)	
Olanzapine			10.3% (46)	
Polypharmacy with clozapine			9.2% (41)	
Quetiapine			9.2% (41)	
Risperidone			7.9% (35)	
Other			7.5% (33)	
Aripiprazole			5.9% (26)	
Haloperidol			3.8% (17)	
Zuclopenthixol LAI			2.7% (12)	
Zuclopenthixol			2.2% (10)	
Paliperidone LAI			2.2% (10)	
Flupentixol			1.1% (5)	
Sulpiride			1.1% (5)	
Any LAI monotherapy[a]			8.3% (37)	
Any FGA monotherapy[a]			16.8% (75)	
Any SGA monotherapy[a]			37.1% (165)	

Where single compounds are mentioned, monotherapy with that compound is meant.
FGA, first-generation antipsychotic; LAI, long-acting injectable antipsychotic; SGA, second-generation antipsychotic.
[a]Excluding clozapine.

(7.9%), oral aripiprazole (5.9%), and oral haloperidol (3.8%). Monotherapy with an LAI was chosen in 8.3% of the switches, whereas polypharmacy without clozapine was chosen in 15.1% of the switches. Polypharmacy with clozapine was chosen in 9.2% of the switches. The number of use periods for all compounds are shown in **Table S1**.

In our main analysis, SGAs were associated with better persistence compared with FGAs (aHR 0.73; 95% confidence interval (CI) 0.57–0.93; $P = 0.011$). No significant difference in persistence was found between monotherapy and polypharmacy in our first secondary analysis (aHR 1.08; 95% CI 0.87–1.35; $P = 0.479$). Both analyses excluded clozapine therapy. The survival curves of the different treatment options (i.e., first vs. second generation and monotherapy vs. polypharmacy) are shown in **Figure 1**.

Compared with starting one of the other antipsychotics, restarting monotherapy clozapine was associated with the best persistence in our final analysis (aHR 0.48; 95% CI 0.32–0.71; $P < 0.001$). Switching to oral monotherapy risperidone (aHR 0.52; 95% CI 0.32–0.84; $P = 0.008$) or oral monotherapy olanzapine (aHR 0.55; 95% CI 0.35–0.87; $P = 0.010$) was also associated with significantly better persistence compared with the other antipsychotics, albeit to a lesser degree than clozapine. Polypharmacy with clozapine was also associated with better persistence compared with monotherapy with the other antipsychotics (aHR 0.46; 95% CI 0.29–0.74; $P = 0.001$). The aHRs of the most used compounds are shown in **Table 2** and the survival curves are shown in **Figure 2**. Two additional analyses were performed, the first of which concerned only the first initiated therapy after the first clozapine

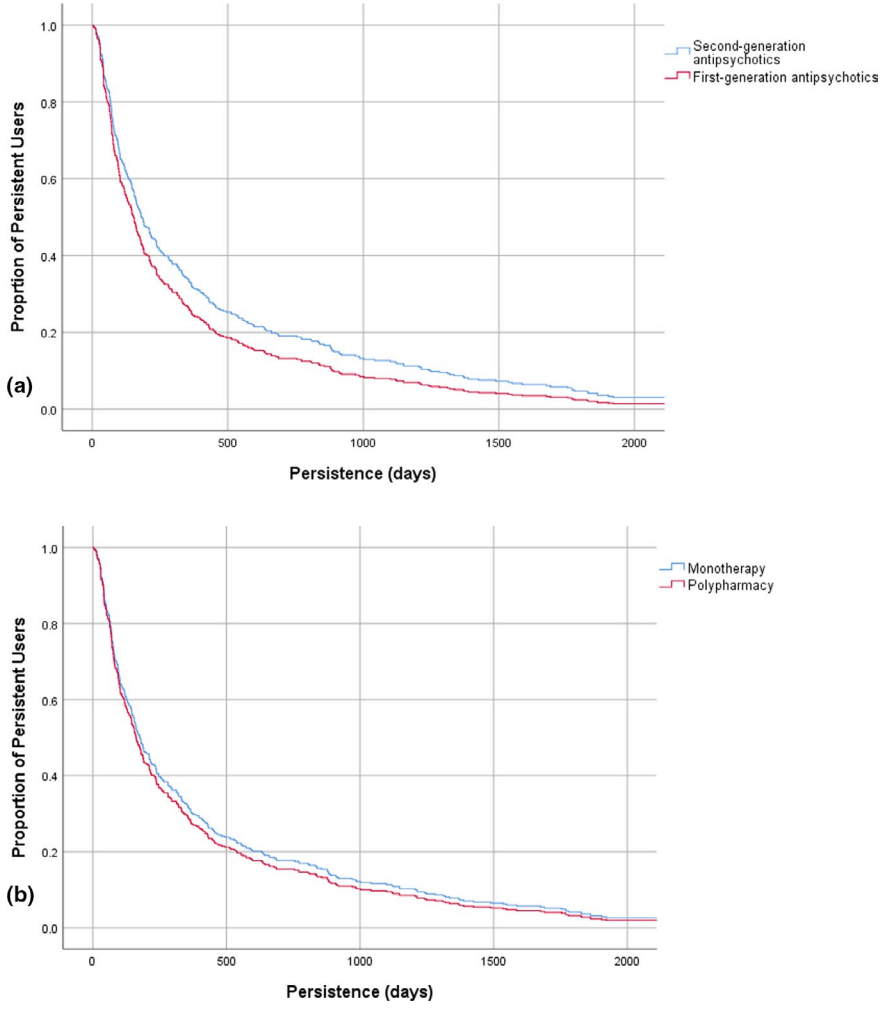

Figure 1 Proportion of users who remain persistent over time. (**a**) Second-generation vs. first-generation antipsychotics (main analysis): second-generation antipsychotics were associated with significantly better persistence than first-generation antipsychotics (adjusted hazard ratio 0.73; 95% confidence interval 0.57–0.93; $P = 0.011$). The compounds (oral and/or long-acting injectable antipsychotic) included in the first-generation antipsychotic-group were haloperidol, zuclopenthixol, flupentixol, levomepromazine, fluphenazine, pimozide, pipamperone, bromperidol, penfluridol, periciazine, tiapride, and thioridazine. The compounds (oral and/or long-acting injectable antipsychotic) included in second-generation antipsychotic-group were clozapine, olanzapine, quetiapine, risperidone, aripiprazole, paliperidone, sulpiride, lurasidone, and sertindole. Restarting clozapine was not included in this analysis. (**b**) Monotherapy vs. polypharmacy (first secondary analysis); no significant difference in persistence was found between monotherapy and polypharmacy (adjusted hazard ratio 1.08; 85% confidence interval 0.87–1.35; $P = 0.48$). Restarting clozapine was not included in this analysis.

Table 2 Risk of nonpersistence in users of monotherapy antipsychotics, polypharmacy with clozapine, and polypharmacy without clozapine after clozapine discontinuation

Antipsychotic compound	aHR [95% CI]	*P* value
Polypharmacy with clozapine	0.46 [0.29–0.74]	**0.001**
Clozapine	0.48 [0.32–0.71]	**3.46×10^{-4}**
Risperidone	0.52 [0.32–0.84]	**0.008**
Olanzapine	0.55 [0.35–0.87]	**0.010**
Aripiprazole	0.60 [0.36–1.01]	0.052
Quetiapine	0.69 [0.44–1.10]	0.119
Polypharmacy without clozapine	0.81 [0.55–1.18]	0.263
Paliperidone LAI	1.46 [0.72–2.98]	0.299
Zuclopenthixol	0.75 [0.37–1.55]	0.441
Zuclopenthixol LAI	0.93 [0.48–1.81]	0.832
Sulpiride	0.87 [0.36–2.38]	0.868
Haloperidol	0.96 [0.53–1.73]	0.888
Flupentixol	1.05 [0.41–2.70]	0.915
Other antipsychotics	1.00 (reference)	

This information is displayed as hazard ratios adjusted for sex and age (aHR), with 95% CIs, ordered from most (top) to least strongly associated with persistent use relative to the group of other antipsychotics with few observations (i.e., levomepromazine, pipamperone, pimozide, periciazine, thioridazine, bromperidol, sertindole, penfluridol, tiapride, paliperidone, lurasidone, fluphenazine LAI, haloperidol LAI, flupentixol LAI, bromperidol LAI, olanzapine LAI, and risperidone LAI). All monotherapy compounds are oral formulations unless indicated with "LAI." Significant results (*P* value < 0.05) that remained significant in the sensitivity analysis with expanded permissible gap are depicted in bold.
aHR, adjusted hazard ratio; CI, confidence interval; LAI, long-acting injectable antipsychotic.

discontinuation, including each patient once. The results show that switching to oral olanzapine (aHR 0.53; 95% CI 0.33–0.86; *P* = 0.010), oral risperidone (aHR 0.42; 95% CI 0.24–0.72; *P* = 0.002), restarting clozapine monotherapy (aHR 0.46; 95% CI 0.30–0.71; *P* < 0.001), or clozapine polytherapy (aHR 0.45; 95% CI 0.28–0.73; *P* = 0.001) are still associated with better persistence compared with switching to other antipsychotics. The second additional analysis performed compared persistence between restarting clozapine within 4–8 months and restarting clozapine within 9–12 months after clozapine discontinuation. No difference was found in persistence between both groups (755 vs. 925 days; *P* = 0.69). Furthermore, only 14 subjects restarted clozapine within 9–12 months after clozapine discontinuation.

Sensitivity analysis

In our sensitivity analysis, the permissible gap was expanded from 30 to 90 days to evaluate the effect of adherence on the persistence results. SGAs remained associated with a significantly better persistence than FGAs (aHR 0.69; 95% CI 0.54–0.90; *P* = 0.005). Similarly, the sensitivity analysis did not show differences between monotherapy and polypharmacy (aHR 1.14; 95% CI 0.91–1.42; *P* = 0.25). Finally, the results for restarting monotherapy clozapine (aHR 0.52; 95% CI 0.35–0.77; *P* = 0.001), switching to oral monotherapy olanzapine (aHR 0.58; 95% CI 0.37–0.90; *P* = 0.016), and switching to oral monotherapy risperidone (aHR 0.54; 95% CI 0.33–0.87; *P* = 0.013) did not change. The results for polypharmacy with clozapine (aHR 0.51; 95% CI 0.32–0.80; *P* = 0.004) did not change either. The aHRs of the most used compounds are provided in **Table S2**.

DISCUSSION

To our knowledge, this is the first drug dispensing study comparing persistence between several antipsychotic treatment options in patients with schizophrenia who discontinue clozapine therapy. We demonstrated that monotherapy with second-generation oral antipsychotics performs best, especially with clozapine, followed by olanzapine and risperidone.

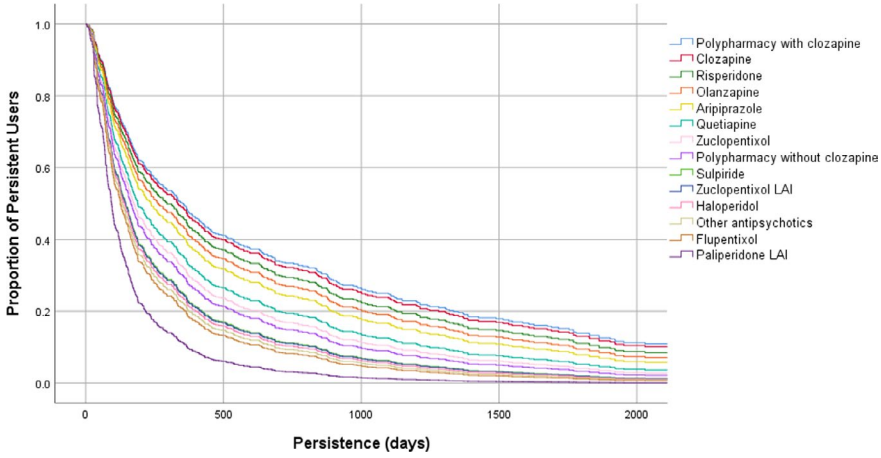

Figure 2 Proportion of antipsychotic users who stay persistent over time, structured per compound associated with the best persistence over time from top to bottom (second secondary analysis, all compounds listed are monotherapies unless "polypharmacy" and all monotherapy compounds are oral formulations unless indicated with long-acting injectable antipsychotic (LAI)): monotherapy with clozapine (adjusted hazard ratio (aHR) 0.48; 95% confidence interval (CI) 0.32–0.71; *P* < 0.001), oral risperidone (aHR 0.52; 95% CI 0.32–0.84; *P* = 0.008) and oral olanzapine (aHR 0.55; 95% CI 0.35–0.87; *P* = 0.010) were associated with significantly better persistence compared with the other antipsychotics. Polypharmacy with clozapine (aHR 0.46; 95% CI 0.29–0.74; *P* = 0.001) was also associated with significantly better persistence compared with monotherapy with the other antipsychotics, whereas polypharmacy without clozapine performed average.

Our analyses indicate that SGAs are associated with better persistence than FGAs in patients discontinuing clozapine for undefined reason. The explanation could be the better efficacy of SGAs, especially regarding negative symptoms, compared to FGAs.[38,43] Another interpretation could be the occurrence of side effects, as SGAs are associated with fewer extrapyramidal symptoms and tardive dyskinesia than FGAs, albeit with more metabolic adverse events.[43] Possibly, patients stopping clozapine prefer the absence of extrapyramidal symptoms over the occurrence of other side effects caused by SGAs. Alternatively, SGAs may be preferred by these patients as they are associated with increased quality of life compared with FGAs in general patients with schizophrenia.[37,44] In the Netherlands, shared decision making concerning the selection of an antipsychotic is common.[45] The current study shows that SGAs are also preferred in patients who discontinue clozapine, particularly clozapine, olanzapine, and risperidone. The observation that restarting clozapine is associated with good persistence of use indicates that clozapine should be reconsidered when it was previously given but discontinued for undefined reasons. Of note, the third most often initiated monotherapy, oral quetiapine, was not associated with better persistence compared with the other antipsychotics. These findings are in line with a recent meta-analysis showing superior symptom reduction of olanzapine and risperidone compared with other antipsychotics, such as quetiapine, in patients with TRS.[16] Quetiapine could be frequently initiated due to the favorable side-effect profile, compared with other antipsychotics.[37] The findings are also in line with a recent Finnish registry study showing that restarting clozapine and switching to oral olanzapine is associated with a lower risk of psychiatric ward re-admission, treatment failure, and mortality, compared with switching to other antipsychotics.[23]

We found that polypharmacy without clozapine was associated with similar persistence relative to monotherapy in patients discontinuing clozapine. Polypharmacy may reduce symptoms more effectively than monotherapy due to better receptor occupancy, but this could also lead to more or relatively severe side effects, resulting in no difference in persistence. Furthermore, there is still a lack of high-quality studies comparing polypharmacy with monotherapy, especially in patients with TRS.[16] Interestingly, patients on polypharmacy who also used clozapine showed the most prolonged persistence of all interventions studied here, with hazard ratios for nonpersistence that were similar to clozapine monotherapy.

The patients included in this study were more likely to be men, which can be explained by the observation that men are more likely to develop schizophrenia than women.[42] However, the male to female incidence ratio in patients with schizophrenia is 1.4:1, whereas the ratio in this study was 1.8:1.[46] This could indicate that male patients are more prone to start clozapine therapy or to discontinue clozapine therapy, possibly due to relatively severe symptomatology, a less favorable course of illness and increased TRS incidence in men with schizophrenia.[47] Additionally, the female participants were significantly older than the male patients included in this study, which may be due to the relatively high age of onset (25–30 years) and a second incidence peak at age 45 in women with schizophrenia.[41]

The primary strength of this study is that a large and representative set of real-life data were used, which reflects clinical practice better than an RCT.[32] However, the current study also has several limitations. First, observational studies like ours may suffer from confounding by indication. Although we cannot rule out that such confounding may play a role in our study population, we found consistent evidence across analyses (including sensitivity analyses) that SGAs are associated with better persistence. Second, the registry used for the current study does not track several variables that could be used as covariates, such as clozapine blood levels to more closely monitor adherence. Furthermore, the results of this study indicate that clozapine re-initiation could be successful in patients who discontinue clozapine. However, clozapine therapy can be discontinued because of serious side effects, such as neutropenia, agranulocytosis, or myocarditis, despite adequate symptom reduction. Research suggests that about 50% of patients with clozapine-associated neutropenia can tolerate clozapine re-challenge.[48] Because no information on the reason of discontinuation was available in this study, it is not known whether clozapine is safe to restart in patients who discontinued due to such adverse events. Research suggests that co-administration of granulocyte colony-stimulating factor could support clozapine re-challenge in patients experiencing neutropenia. Unfortunately, no information on granulocyte colony-stimulating factor use was available for the current cohort.[49] On a similar note, previous rehospitalizations, comorbidities, use of nonpharmacological treatment options, duration of illness, and disease severity are not entered into the database, precluding the incorporation of such variables as covariates in our model. Information on relocating of patients and, therefore, exiting the database, was unavailable, resulting in right-censoring. Moreover, it is unknown if a patient used medication and how many compounds were used before entering the database. That is why the number of compounds used before starting clozapine was not incorporated as a covariate in our model. Another limitation of this study is that drug dispensing data was used, which does not guarantee that patients actually adhered to the medication dispensed to them. Finally, few participants used LAI antipsychotics after clozapine discontinuation, hampering the examination of individual LAI antipsychotics.

In conclusion, the results of this study suggest that for subjects who discontinued clozapine due to undefined reasons, clinicians should consider oral monotherapy with SGAs, particularly clozapine (except in those patients with previous serious adverse reactions to clozapine), olanzapine, and risperidone. Researchers designing RCTs for this vulnerable patient group may consider our findings to prioritize the compounds to be investigated.

Supporting Information. Supplementary information accompanies this paper on the *Clinical and Translational Science* website (www.cts-journal.com).

Funding. No funding was received for this work.

Conflict of Interest. J.T., H.T. and A.T. have participated in research projects funded by grants from Janssen-Cilag and Eli Lilly to their employing institution. Jari Tiihonen reports personal fees from the Finnish Medicines Agency (Fimea), European Medicines Agency (EMA), Eli Lilly, Janssen-Cilag, Lundbeck, and Otsuka; is a member of advisory board for Lundbeck, and has received grants from the Stanley Foundation and Sigrid Jusélius Foundation. All other authors report no conflicts of interest.

Author Contributions. N.S., J.J.L., J.T., H.T., A.T., and C.P. wrote the manuscript. N.S., J.J.L., J.T., H.T., A.T., and C.P. designed the research. N.S., L.I., C.V., J.B., and B.B. performed the research. N.S. and L.I. analyzed the data.

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