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ORIGINAL RESEARCH

Relationship between the timing of relapse and plasma drug levels following discontinuation of cariprazine treatment in patients with schizophrenia: indirect comparison with other second-generation antipsychotics after treatment discontinuation

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Objective: To explore the timing of relapse following drug discontinuation and its relationship to estimated plasma levels and elimination half-life by comparing data from a randomized, placebo-controlled discontinuation study of cariprazine with those from similarly designed and conducted randomized control trials of other oral atypical antipsychotics (AAPs).

Methods: Data from a long-term, randomized, double-blind, placebo-controlled relapse prevention study in participants with schizophrenia (NCT01412060) were analyzed. Similarly designed, published studies of other AAPs were used for comparison. Time to drug-placebo relapse separation and relapse rates were estimated from Kaplan–Meier curves and evaluated descriptively. Separation was defined as a sustained difference of ≥5% incidence of relapse between the AAP and placebo curves.

Results: The Kaplan–Meier curve for cariprazine showed a time to drug-placebo relapse separation at 6–7 weeks after randomization, compared to the Kaplan–Meier curves for the other AAPs, which showed earlier separation at 1–4 weeks. The placebo relapse rates at 4 weeks after randomization were 5% for cariprazine and 8–34% for other AAPs. Geometric mean values of model-predicted plasma concentrations for total active cariprazine moieties (sum of cariprazine, desmethyl-cariprazine, and didesmethyl-cariprazine) were 20.0 and 6.1 nM at 2 and 4 weeks after discontinuation, respectively. Elimination half-lives of other AAPs and their active metabolites (<4 days) suggest that plasma concentrations would be low or negligible at 2–4 weeks after last dose.

Conclusion: Discontinuation of cariprazine treatment appeared to be associated with a delayed incidence of relapse compared with other AAPs, which may be due to the longer half-life of cariprazine and its active metabolites.

Keywords: cariprazine, schizophrenia, half-life, occupancy

Introduction

Schizophrenia is a severe, chronic, and heterogeneous disorder that has a profound impact on the health, social, and economic well-being of patients, families, caregivers, and society.[1,2] Relapse prevention is critical for improving long-term outcomes in patients with schizophrenia.[3] Randomized, placebo-controlled, double-blind trials have demonstrated that continued antipsychotic treatment was significantly

more effective than drug discontinuation for relapse prevention (number needed to treat [NNT]=3–5).[3] However, partial adherence and nonadherence are key threats to symptomatic stability and functional achievements,[4] and these rates have been reported to be as high as 50%, which can limit the efficacy of pharmacotherapy.[5,6] Factors contributing to partial adherence and nonadherence include patient knowledge, attitudes toward their illness and the medication, and past experiences with their illness and its treatment.[7] Furthermore, the medical cost of partial adherence and nonadherence is estimated to be approximately 40% of health care spending for schizophrenia.[8]

Long-acting injectable antipsychotics (LAIs) have shown superiority over oral antipsychotics in preventing hospitalization in real-world mirror-image[9] and cohort[10] studies. Since pharmacologic characteristics of LAIs and oral antipsychotics are equivalent, it is believed that the superiority of LAIs in these studies is due to assured medication delivery, as nonadherence is apparent upon missing an injection, and LAIs have substantially longer half-lives compared with oral agents.[11] Supporting the concept that the half-life of pharmacotherapy may be important in preventing relapse, a study comparing the effect of oral versus LAI formulations of paliperidone found that patients who withdrew from treatment remained relapse-free longer if they had been treated with an LAI versus oral formulation.[12] Despite the potential advantages of LAIs, oral antipsychotics are considered to be the first-line treatment and are more commonly prescribed than LAIs. This may be due to negative attitudes toward LAIs (eg, side effects, costs) and clinicians primarily prescribing LAIs to patients with chronic schizophrenia and a history of partial adherence or nonadherence and/or multiple relapses.[13,14] It has also been hypothesized that oral atypical antipsychotics with longer half-lives, in a manner similar to LAIs, may be able to bridge gaps in appropriate medication intake by providing prolonged drug exposure during periods of decreased adherence.[15]

Cariprazine, an oral dopamine D_3-preferring D_3/D_2 receptor partial agonist, serotonin 5-HT$_{1A}$ receptor partial agonist, and 5-HT$_{2A}$ receptor antagonist,[16] is approved for the treatment of adults with schizophrenia (US and Europe) and adults with manic, mixed, or depressive episodes of bipolar I disorder (US). Cariprazine forms two major metabolites, desmethyl-cariprazine (DCAR) and didesmethyl-cariprazine (DDCAR), which are pharmacologically equipotent to and have relatively similar in vitro binding profiles compared with cariprazine.[17,18] Half-lives based on time to reach steady state are 2–4 days for cariprazine, 1–2 days for DCAR, and 1–3 weeks for DDCAR; the effective half-life of total CAR (molar sum of cariprazine, DCAR, and DDCAR) is approximately 1 week.[17] At steady state, the most prominent moiety is DDCAR, distantly followed by cariprazine and then DCAR.

In contrast to cariprazine and its active metabolites, the half-lives of all other oral antipsychotics are considerably shorter, in the range of 7–91 hrs (eg, aripiprazole, asenapine, brexpiprazole, iloperidone, lurasidone, olanzapine, paliperidone, quetiapine, ziprasidone);[15] the half-lives of their active metabolites are on the same order of magnitude as the parent drug. An exception is risperidone, which has a half-life of 3 hrs, whereas its active metabolite, 9-OH risperidone (paliperidone), has an approximate half-life of 25 hrs,[19] which is consistent with most other once-daily oral antipsychotics.

The overall objective of this post hoc, exploratory study was to investigate if there could be a connection between the timing of relapse following drug discontinuation and estimated plasma levels (and/or elimination half-life) by comparing data from a randomized, placebo-controlled discontinuation study of cariprazine with those from similarly designed and conducted randomized, controlled trials of other oral atypical antipsychotics.

Methods
Cariprazine relapse prevention study design

Data from a long-term, randomized, double-blind, fixed-dose, placebo-controlled relapse prevention study in participants with schizophrenia (NCT01412060) were analyzed; detailed methods for this study are published elsewhere.[20] Briefly, participants stabilized with cariprazine during a 20-week open-label phase were randomized (1:1) to continue cariprazine (3, 6, or 9 mg/d) or switch to placebo for up to 72 weeks of double-blind treatment. In order to continue to double-blind treatment, participants were required to meet the following stabilization criteria: Positive and Negative Syndrome Scale (PANSS)[21] total score ≤60; decrease from baseline ≥20% in PANSS total score; Clinical Global Impressions-Severity of Illness (CGI-S)[22] score ≤4; score ≤4 on each of the 7 PANSS items (delusions, conceptual disorganization, hallucinatory behavior, suspiciousness/persecution, hostility, uncooperativeness, and poor impulse control); and no significant

tolerability issues (investigator judged). The primary outcome for the relapse prevention study was time to relapse during double-blind treatment. The *P*-value was based on the log-rank test; HR and 95% CI were based on Cox proportional hazards regression model, with treatment group as an explanatory variable.

Relapse was defined by objective rating scale criteria and subjective clinical measures. Participants were deemed as relapsed if they met any of the following rating scale criteria: increase ≥30% in PANSS total score for participants who scored ≥50 at randomization or increase ≥10 in PANSS total score for participants who scored <50 at randomization; score >4 on any of the 7 PANSS items (defined above); CGI-S score ≥2 point increase from randomization. Relapse was also judged to occur if, in the investigator's opinion, the participant was hospitalized due to worsening of schizophrenia; exhibited deliberate self-injury or aggressive/violent behavior; or had clinically significant suicidal/homicidal ideation.

This study was conducted in compliance with the International Conference on Harmonisation Guidances on General Considerations for Clinical Trials and Good Clinical Practice and the Declaration of Helsinki. This study was also approved by institutional review boards or ethics committees and government agencies (Table S1). All participants provided written informed consent after receiving a complete description of the studies.

Relapse prevention study designs for the other oral atypical antipsychotics

Data from published, similarly designed relapse prevention studies of other oral antipsychotics[23–29] were used for comparison. In these studies, the primary outcome measure was time from randomization to relapse or impending relapse analyzed using standard statistical methods (eg, log-rank test); relapse and stability criteria were defined similarly to the cariprazine study (Table S2) and participants were required to meet stabilization criteria before proceeding to the next study phase (eg, stabilization to randomized). Across studies, length of stabilization phase ranged from 8 to 36 weeks, and double-blind, randomized phase was placebo-controlled and ranged from 16 to 52 weeks; however, due to the limited number of studies available, these factors could not be rigorously evaluated. Two placebo-controlled, discontinuation studies (aripiprazole and ziprasidone)[30,31] were excluded from these analyses because the studies did not include a stabilization

phase on the tested antipsychotic; rather, the enrolled participants had been stabilized on any antipsychotic and were then switched to either aripiprazole or ziprasidone, or to placebo.

Relapse analyses

Kaplan-Meier (K-M) curves from published relapse prevention studies of oral antipsychotics were used to estimate the time to curve separation between drug and placebo relapse rates. Separation was defined as a sustained difference of ≥5% incidence of relapse between drug and placebo curves; the 5% cutoff was selected because this threshold was roughly the point at which participants being treated with the drug generally had a significantly lower incidence of relapse compared with those being treated with placebo. A sensitivity analysis using a 10% cutoff, which corresponds to NNT≤10, was also performed to provide a threshold of established clinical relevance.[32] In addition, a post hoc analysis of the cariprazine study was conducted to evaluate the time to curve separation in the subset of participants who were stabilized on 3–6 mg/d cariprazine (doses within the US Food and Drug Administration [FDA] and European Medicines Agency [EMA] recommended dose range).

Plasma concentrations of total CAR were obtained from participants who were randomized to placebo in the cariprazine study by using individual-level predictions derived from population pharmacokinetic models.[33] Elimination half-lives of oral antipsychotics and their active metabolites, if available, were obtained from the prescribing information of each drug; these values were used to estimate plasma concentrations after drug discontinuation. The proportions of each active moiety at steady state (relative to total active moieties) were calculated using mean trough plasma or serum concentrations,[34–38] but if this information was not available, then proportions were obtained from the literature or the drug's prescribing information. Study characteristics such as stability criteria, length of open-label stabilization phase, and discontinuation protocol were evaluated descriptively for between-study differences.

Analyses compared the time to drug-placebo relapse separation of 5% and 10%; differences in time to drug-placebo relapse separation and placebo relapse rates at 4 weeks after randomization between each oral antipsychotic and their respective placebo group were compared across drugs descriptively. The time to drug-placebo relapse separation was also compared with the time at which PANSS total scores separated between drug and placebo (if information was published). The potential relationship

between delayed relapse (eg, time to drug-placebo relapse separation and placebo relapse rates) and weighted elimination half-life was evaluated by visual inspection. Weighted elimination half-life is the summation of each drug and, if applicable, the active metabolite's elimination half-life multiplied by its proportion at steady state relative to total active moieties; for ranges, the median was used. A sensitivity analysis was also performed using the longest reported elimination half-life or elimination half-life of the most prominent moiety at steady state of each drug. Statistical analysis could not be performed to evaluate between-study differences due to the limited number of available studies.

Results

This analysis included eight published placebo-controlled relapse prevention studies of oral atypical antipsychotics that had an open-label stabilization phase (8–36 weeks); a summary of these studies is presented in Table 1. All studies required participants to meet stability criteria prior to continuing to the randomized, double-blind phase (Table 1, Table S2). Five studies[23,25–28] required participants to meet

stability criteria for >8 continuous weeks; the other three studies[20,24,29] required participants to meet stability criteria at prespecified time points. Only one study[24] tapered discontinuation to placebo; all others were assumed to have used an abrupt discontinuation protocol.

Cariprazine treatment (3–9 mg/d) was associated with a significantly delayed time to relapse compared with placebo (P=0.0039, HR [95% CI]=0.52 [0.33, 0.82]).[39] An analysis was also performed to evaluate the time to relapse in a subgroup of participants that received doses of cariprazine within the FDA- and EMA-recommended range (1.5–6 mg/d). Treatment with cariprazine doses within this range (ie, 3–6 mg/d) was also associated with a significantly delayed time to relapse compared with the corresponding placebo group (ie, participants that were stabilized on cariprazine 3–6 mg/d during the open-label phase; P=0.026, HR [95% CI]=0.49 [0.25, 0.93]). In all studies of other oral antipsychotics, treatment with drug compared with placebo was also associated with a significantly delayed time to relapse or impending relapse (P<0.05 for all).[23–29]

The K-M curve for cariprazine treatment (3–9 mg/d) showed a time to drug-placebo relapse separation at

Table 1 Relapse prevention study characteristics

Study	Stabilization		Stability criteria[b]	Number of DB patients	DB length (weeks)
	Design	Length (weeks)[a]			
Asenapine[27]	OL	26	26 weeks continuous	ASE=194 PBO=192	26
Brexpiprazole[23]	SB	12–40	12 weeks continuous	BRX=97 PBO=105	<52[c]
Cariprazine[20]	OL	20	Meet at weeks 8 and 20	CAR=101 PBO=99	26–72
Iloperidone[28]	OL	15–25	12 weeks continuous	ILO=153 PBO=150	<26[c]
Lurasidone[26]	OL	12–24	12 weeks continuous	LUR=144 PBO=141	28
Olanzapine[25]	OL	8–14	8 weeks continuous	OLZ=224 PBO=102	<30[c]
Paliperidone ER[29]	OL	14	Meet at weeks 8 and 14[e]	PAL=105 PBO=102	16–40[c]
Quetiapine XR[24,d]	OL	16	Meet at weeks 8 and 16	QTP=94 PBO=103	≤39[c]

Notes: [a]Length includes cross-titration, run-in, and stabilization periods, if applicable, and ranges indicate that patients could move to randomization phase once stability criteria were met; [b]details on stability criteria are provided in Table S1; [c]variable length is due to positive interim results and subsequent early study termination; [d]QTP XR was the only study that had a tapered discontinuation protocol (4-day cross titration); [e]stability criteria obtained from https://clinicaltrials.gov/ct2/show/NCT00086320.
Abbreviations: ASE, asenapine; BRX, brexpiprazole; CAR, cariprazine; DB, double-blind; ER or XR, extended release; ILO, iloperidone; LUR, lurasidone; OL, open-label; OLZ, olanzapine; PAL, paliperidone; PBO, placebo; QTP, quetiapine; SB, single-blind.

6.6 weeks after randomization (Figure 1A); this correlated with time to separation of PANSS total score change between cariprazine and placebo (Figure S1). For participants stabilized in the recommended 3–6 mg/d dose range, the K-M curve showed that time to drug-placebo relapse separation occurred even later, at 8.3 weeks, when compared with its corresponding placebo group (Figure 1B).

K-M curves from studies of other oral antipsychotics showed earlier separation between drug and placebo, ranging between 1 and 4 weeks (Table 2). Two of these studies published by-week PANSS total score data; in those studies, time to drug-placebo relapse separation also coincided with the between-group separation of PANSS total score change (lurasidone: ~3 weeks vs 4 weeks, respectively; paliperidone ER: 1.6 weeks vs 1 week, respectively).[26,29]

In the cariprazine study, overall placebo relapse rate at week 4 was estimated to be 5%; the estimated placebo relapse

rates for the other oral antipsychotics were higher, ranging from 8% to 34% at 4 weeks after last dose (Table 2). Brexpiprazole, with the second longest half-life after cariprazine, had the second lowest placebo relapse rate and second longest time to drug-placebo relapse separation. The remainder of the oral antipsychotics all had half-lives of approximately 1 day or less; correspondingly, these compounds had the highest placebo relapse rates at week 4 and shortest time to drug-placebo relapse separation following treatment discontinuation.

Placebo relapse rate and time to drug-placebo relapse separation appeared to be correlated with elimination half-life (Table 2); a graphical representation plotting relapse outcomes versus weighted elimination half-life is shown in Figure 2. A similar trend was seen for time to drug-placebo separation with clinically relevant separation defined as $\geq$10% sustained difference (equivalent to an NNT=10) compared with separation defined as $\geq$5% sustained (Figure 2B-C; Table 2). Analyses were performed using the longest drug or metabolite elimination half-life, as well as using median elimination half-life of the most prominent moiety instead of weighted half-life; results were similar regardless of half-life calculation method (data not shown).

Geometric mean values of model-predicted plasma concentrations for total CAR were 20.0 and 6.1 nM at 2 and 4 weeks after last cariprazine dose, respectively (Figure 3). Based on published EC_{50} estimates for D_2 and D_3 receptor occupancy by total CAR, which are 13.0 and 3.8 nM, respectively,[40] D_2 and D_3 receptors are predicted to remain occupied at 2 and 4 weeks after last cariprazine dose. Geometric mean values of model-predicted plasma concentrations for DDCAR, which is the most prominent moiety at steady state, were 18.5 and 5.5 nM at 2 and 4 weeks after last cariprazine dose, respectively. Elimination half-lives of other oral antipsychotics and their active metabolites (Table 2) suggest that plasma concentrations and D_2 and D_3 receptor occupancy for those compounds would be low or negligible at 2 and 4 weeks after last dose.

Discussion

This analysis examined the relationship between the trajectories of the incidence of relapse and the plasma concentrations of oral antipsychotics in participants with schizophrenia after drug discontinuation (eg, randomization to double-blind placebo). In all of the relapse prevention studies that were included in this post hoc, exploratory study, treatment with oral antipsychotics was significantly superior versus placebo at delaying schizophrenia relapse or
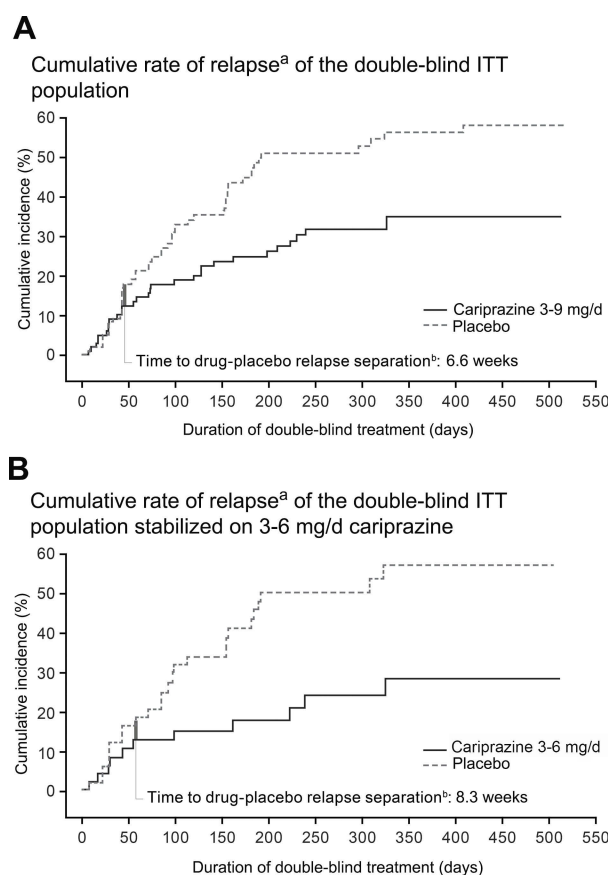
A

Cumulative rate of relapse[a] of the double-blind ITT population

B

Cumulative rate of relapse[a] of the double-blind ITT population stabilized on 3-6 mg/d cariprazine

Figure 1 Cumulative rate of relapse.
Notes: [a]Kaplan–Meier curves for time to relapse in the final intent-to-treat (ITT), randomized population during the double-blind period for cariprazine 3–9 mg/d versus the overall placebo group (**A**) and for cariprazine 3–6 mg/d versus its corresponding placebo group (**B**); [b]thick vertical bar represents 5% incidence of relapse and indicates the time to drug-placebo relapse separation. Panel A is adapted from © 2019 Allergan. Used with permission.

Table 2 Placebo relapse rate, time to drug-placebo relapse separation, and elimination half-lives of drugs and major active metabolites

Drug	PBO relapse at week 4 (%)[a]	Time to drug-PBO relapse separation (weeks)[a]		Elimination half-life of drug and major active metabolites[b]	Proportion[c] at steady state of drugs and active metabolites
		5% Separation	10% Separation		
CAR	5	6.6	12.0	CAR: 2–4 days DCAR: 1–3 days DDCAR: 1–3 weeks[d]	CAR: 23.3% DCAR: 7.2% DDCAR: 69.5%[e]
BRX	8	4.0	6.1	BRX: 91 hrs	No CNS active metabolites
QTP XR[f]	13	2.7	3.4	QTP: 7 hrs Norquetiapine: 12 hrs	QTP: 30.3–35.7% Norquetiapine: 64.3–69.7%[g]
OLZ	15	2.6	4.1	OLA: 30 hrs	No CNS active metabolites
LUR	15	2.7	8.2	LUR: 18 hrs ID-14283: 7.5–10 hrs[h]	LUR: 70% ID-14283: 26%[i]
ASE	18	1.1	2.4	ASE: ~24 hrs	No CNS active metabolites
ILO	24	1.1	3.3	ILO: 18–33 hrs P95: 23–31 hrs P88: 26–37 hrs	ILO: 32.5% P95: 48% P88: 19.5%[j]
PAL ER[f]	34	1.6	3.3	PAL ER: 23 hrs	No CNS active metabolites

Notes: [a]Estimated from final intent-to-treat population Kaplan–Meier curve; separation was defined as a sustained difference of ≥5% or ≥10% incidence of relapse between drug and placebo curves; [b]elimination half-life values were obtained from the prescribing information of each drug unless otherwise specified; [c]proportion of drug and active metabolites is relative to total active moieties; [d]elimination half-lives for cariprazine, DCAR, and DDCAR are based on time to steady-state values; [e]proportions calculated using model-predicted C_{min} values at steady state from a population pharmacokinetic modeling study (A.P. and T.C., unpublished data, 2014); [f]please note that QTP XR and PAL ER are sustained-release formulations; [g]proportions calculated using serum concentrations from Bakken et al (2011)[35] and Bakken et al (2015)[34] with the assumption that steady-state pharmacokinetic parameters are similar for the IR and XR formulations as reported by Bui et al (2013);[36] [h]elimination half-life for ID-14,283 was obtained from Citrome (2011);[37] [i]proportions are from Meyer et al (2009)[38] and based on mean serum concentrations; [j]proportions at steady state are from extensive metabolizers in the prescribing information for ILO.
Abbreviations: ASE, asenapine; BRX, brexpiprazole; CAR, cariprazine; CNS, central nervous system; DCAR, desmethyl-cariprazine; DDCAR, didesmethyl-cariprazine; ER or XR, extended release; ILO, iloperidone; LUR, lurasidone; OLZ, olanzapine; PAL, paliperidone; PBO, placebo; QTP, quetiapine.

impending relapse.[20,23-29,39] This study found that there was a delayed incidence of schizophrenia relapse following discontinuation of cariprazine treatment relative to discontinuation of treatment with the other oral antipsychotics as reported in separate studies. The incidence of relapse at 4 weeks following discontinuation of cariprazine treatment (5%) was approximately 2–7 times lower than that observed following drug discontinuation in other relapse prevention studies (8–34%). In addition, time to separation between cariprazine and placebo for estimated relapse incidence was 6.6 weeks compared with 1–4 weeks in the other studies. For all oral antipsychotics, the lower placebo relapse rate at week 4 and the longer time to drug-placebo relapse separation were associated with a longer elimination half-life. Factors other than half-life, such as length of open-label stabilization phase and type of drug discontinuation protocol, were relatively consistent across studies. These factors do not appear to be differentiating factors for relapse rate

trajectories in the placebo group or time to drug-placebo relapse separation following antipsychotic discontinuation; however, due to the limited number of studies available, a rigorous evaluation could not be performed. Although the primary analysis in the cariprazine study included some participants who received a cariprazine dose outside the recommended range (9 mg/d), time to drug-placebo relapse separation for the approved dose range of 3–6 mg/d was even longer compared with the 3–9 mg/d dose range, suggesting that the 9 mg/d dose was not a differentiating factor for the delayed time to drug-placebo relapse separation. Overall, relapse occurred in 49.5% of placebo- and 29.7% of cariprazine-treated participants.[39] The relapse rates at the study endpoint on active medication in the cariprazine study are similar to what has been reported in a meta-analysis of relapse prevention studies in schizophrenia, which found that antipsychotics (27%) significantly reduced relapse rates at 1 year versus placebo (64%);[3] thus, the overall
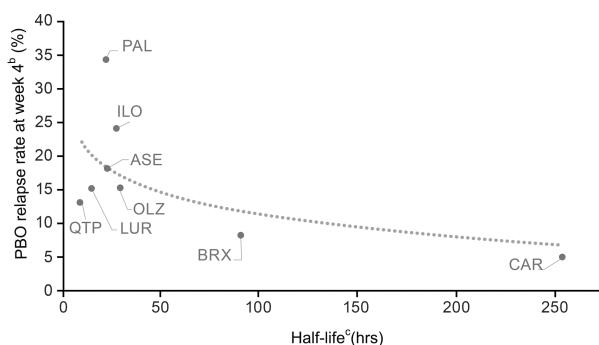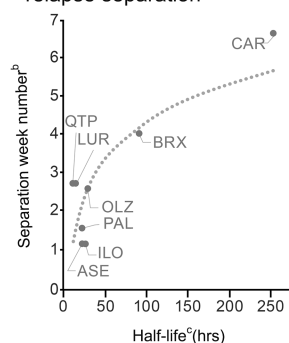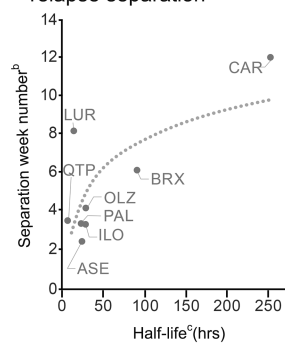
A Placebo relapse rate at week 4 after discontinuation[a]

B Time to 5% drug-placebo relapse separation[a]

C Time to 10% drug-placebo relapse separation[a]

Figure 2 Drug half-life versus placebo relapse rate (**A**) and separation from active drug (**B-C**).
Notes: [a]Logarithm regression fits were generated to provide a visual guide; [b]estimated from final intent-to-treat population Kaplan–Meier curve; [c]weighted half-life values based on elimination half-life and steady-state proportions of each drug (and its metabolites) were used (Table 2).
Abbreviations: ASE, asenapine; BRX, brexpiprazole; CAR, cariprazine; ILO, iloperidone; LUR, lurasidone; OLZ, olanzapine; PAL, paliperidone; PBO, placebo; QTP, quetiapine.

relapse rate also does not appear to be a differentiating factor for the delayed relapse seen after the discontinuation of cariprazine.

The long half-life of cariprazine is primarily due to the presence of an active metabolite (DDCAR) with an extended half-life (1–3 weeks) that is considerably longer than that of the parent drug (2–4 days). In contrast, half-lives for the active metabolites of the compared antipsychotics are approximately the same as that of the parent drug (<4 days). At steady-state and under fixed-dosing conditions, DDCAR is the most prominent moiety (Table 2).[33] Based on the geometric mean values of model-predicted plasma concentrations of DDCAR and its relative value to total CAR, the presence of DDCAR alone may be enough to occupy D_2 and D_3 receptors at 2 and 4 weeks after last dose.

Occupancy of dopamine receptors is believed to be the main mechanism of action for antipsychotics.[41,42] It is believed that 65–80% occupancy of striatal dopamine receptors is associated with optimal therapeutic efficacy, although an analysis of the CATIE trial found that over half of the patients in remission had D_2 occupancy levels below 65%.[43] This observation may suggest that during maintenance treatment, lower levels of D_2 occupancy may be sufficient to delay relapse and provide maintained treatment benefits for stabilized patients. In the cariprazine study, predicted plasma concentrations of total CAR suggest that patients who have discontinued from cariprazine treatment may have substantial D_2 occupancy at 2 weeks after last dose and moderate D_2 occupancy at 4 weeks after last dose. Additionally, plasma concentrations of cariprazine indicate that D_3 receptors are substantially occupied at 2 and 4 weeks after last dose; while it is unknown what roles D_3 receptors have in relapse prevention in patients with schizophrenia, it is believed that they may be involved in modulating cognition, mood, reward, and negative symptoms.[42,44–46]

Relapse can be decreased by uninterrupted pharmacotherapy,[47] but in reality, most outpatients are only partially adherent to their medication regimen.[48,49] After an initial hospital stay, schizophrenia and other psychotic disorders are the leading cause of 7-day readmission and third leading cause of 30-day readmission.[50] In several naturalistic studies, nonadherence rates in patients with schizophrenia ranged from 30% to 60%; however, these numbers appear to drop to approximately 10% or lower in randomized clinical trials where selected patients agreeing to take part in a research study are monitored by health care professionals and have regular access to health care.[7] This finding indicates that better measures are needed in real-world settings to deliver continued treatment to patients on a regular basis. LAIs were introduced as a possible solution; however, not all patients are willing to take an LAI, and despite having been on the market for several years, their usage rate among patients with schizophrenia still pales in comparison to oral antipsychotics.[13] Thus, given the evidence seen with LAIs,[9–12] oral medications that can provide the patient with sufficient coverage from when they are discharged from the hospital to the time of their first outpatient appointment may be able to reduce rates of relapse and rehospitalization. Half-lives of LAIs range from 4–6 days (eg, risperidone-LAI) to 1–2 months for other LAIs (eg, aripiprazole-LAI [30–57 days], paliperidone-LAI [24–49 days], olanzapine-LAI [approximately 30 days]).[51–55] With an effective half-life of approximately 1 week and occupancy of dopamine receptors for up to 4 weeks after the last dose, cariprazine may be an example of an oral antipsychotic that can effectively bridge gaps to provide more beneficial medication coverage.
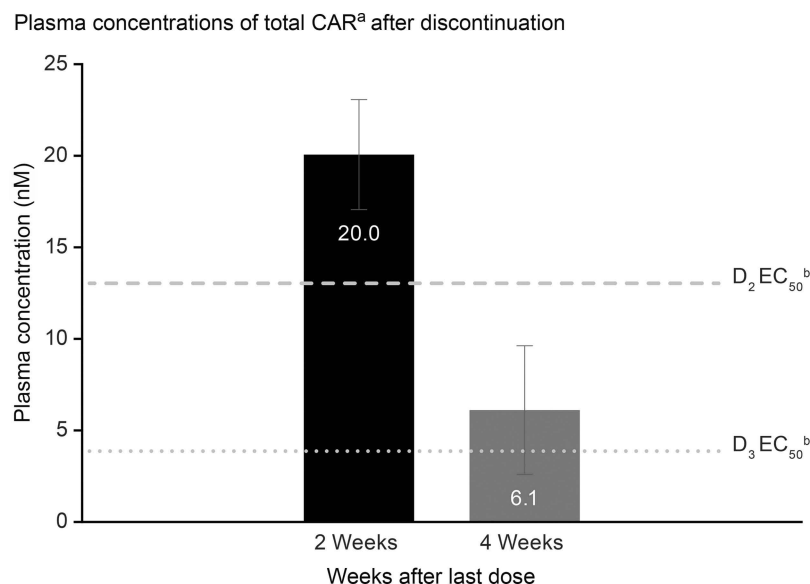
Plasma concentrations of total CAR[a] after discontinuation

Figure 3 Plasma concentrations of total CAR[a] after discontinuation.
Notes: [a]Geometric mean values (geometric SD) of model-predicted total CAR (combined cariprazine, DCAR, and DDCAR) plasma concentrations in patients randomized to placebo during double-blind period; these predicted values are in line with observed data from a pharmacokinetic clinical study;[17] [b]EC_{50} values for D_2 and D_3 receptor occupancy were obtained from Girgis et al (2016).[40]
Abbreviations: DCAR, desmethyl-cariprazine; DDCAR, didesmethyl-cariprazine; total CAR, combined cariprazine, DCAR, and DDCAR.

Results from this study need to be interpreted within its limitations. For example, time to drug-placebo relapse separation and placebo relapse rate were estimated from published K-M curves since primary data were not available for analysis. Another limitation is the lack of standardized definition of curve separation. For this study, 5% and 10% separation were used; however, it is possible that the results may be affected if a different percent separation value was used. It should also be noted that in the cariprazine study, participants received 20 weeks of open-label cariprazine and were at steady-state dosing by the time of randomized withdrawal; as such, it is unclear how relapse rates would change if cariprazine was taken on an inconsistent basis and then abruptly discontinued. Further, the beneficial property of delayed relapse is not well understood and has not been empirically validated. Additionally, due to differences in study designs between the cariprazine relapse prevention study and published studies of some oral antipsychotics, these analyses should be interpreted cautiously and could not include comparisons with some frequently used oral antipsychotics (eg, aripiprazole, ziprasidone) as published studies with a similar design were not available. Future head-to-head, prospective, randomized clinical trials are needed to confirm the results of this post hoc, exploratory study.

In conclusion, the delayed incidence of relapse seen after discontinuation of cariprazine compared with other oral atypical antipsychotics appears to be at least partially due to the particularly long half-life of cariprazine and its active metabolites, which is substantially longer than the half-life of the other oral atypical antipsychotics and their active metabolites. Results from this analysis suggest that the long half-life of cariprazine may result in additional protection from schizophrenia relapse in cases of partial adherence, though prospective comparative trials are needed to confirm these results.

Availability of Data and Material

Allergan will share de-identified patient-level data and/or study-level data, including protocols and clinical study reports, for this clinical trial. To request access to the data, the researcher must sign a data use agreement. All shared data are to be used for non-commercial purposes only. More information can be found on http://www.allerganclinicaltrials.com/.

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Author Contributions

All authors contributed to data analysis, drafting or revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

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Supplementary materials

Table S1 List of independent ethics committee and institutional review boards

Country	Independent ethics committees/institutional review boards
USA	Copernicus Group Sharp Healthcare IRB University of Texas - Houston Health Science Center Office of Research Support Committees
India	Ethics Committee, Shanti Nursing Home, Society for Psychiatric Update and Research IMS - Independent Ethics Committee Ethical Committee Sheth VS Hospital Institutional Ethics Committee, Office of Research Cell, C.S.M. Medical University Vijayawada Institute of Mental Health and Neurosciences Hospital – Ethics Committee Clinic Ethics Forum DMHC Ethics Committee Independent Ethics Committee, 57, Brahmin Mitra Mandal Society Kanpur Medical Ethics Committee Safe Search Independent Ethics Committee Yash Society Ethics Committee Ethics Committee, Radianz Healthcare and Research Central Ethics Committee, Nitte University Manipal University Ethics Committee, Manipal University The Ethics Committee, R.K. Yadav Memorial Mental Health and De-addiction Hospital
Romania	Academia de Stiinte Medicale, Comisia Nationala de Bioteca a Medicamentului si a Dispozitivelor Medicale Comisia Nationala de Etica pentru Studiul Clinic al Medicamentului
Slovak Republic	Eticka komisia NsP sv.Barbory Roznava a.s, Eticka komisia pri LNsP MUDr. Ivana Stodolu Liptovsky Mikulas, Eticka komisia Vseobecnej nemocnice Rimavska Sobota NaP Eticka komisia Fakultnej nemocnice Trnava Eticka komisia Univerzitnej nemocnice Ruzinov Bratislava Eticka komisia LF UK a Univerzitnej nemocnice
Ukraine	Ethics Commission at Kyiv City Clinical Psychoneurological Hospital #1 Ethics Commission of Kyiv City Psychoneurological Hospital #2 Ethics Commission of Communal Institution Lviv Regional Clinical Psychiatric Hospital The Ethics Commission of State Medical and Preventive Institution Central Clinical Hospital of Ukrzaliznytsia Ethics Committee of the Kharkiv Regional Clinical Psychiatric Hospital #3 Ethics Commission at SE Institute of Neurology, Psychiatry and Narcology of NAMS of Ukraine Ethics Commission of Communal Institution Kherson Regional Psyciatric Hospital of Kherson Regional Council Ethics Commission at Communal Institution O.I. Yushchenko Vinnytsia Regional Psychoneurologic Hospital Ethics Commission of Crimea Republic Institution Psychoneurological Dispensary Ethics Commission of Communal Institution Dnipropetrovsk Clinical Psychiatric Dnipropetrovsk Regional Council Ethics Commission at Crimea Republic Institution Clinical Psychiatric Hospital #1 Ethics Commission at City Clinical Psychoneurological Hospital #1 Ethics Commission at Communal Therapeutic and Preventative Institution "Regional Clinical Psychiatric Hospital" Ethics Commission at Odessa Regional Medical Centre of Mental Health Ethics Committee of Regional Psycho-Neurological Hospital #3

Table S2 Detailed stability criteria used in the relapse prevention studies

Drug	Checkpoints	Stability criteria
CAR[1]	Meet at week 8/20	PANSS total score≤60; ≥20% decrease in PANSS total score from baseline; CGI-S≤4; score≤4 on each of the 7 PANSS items (delusion, conceptual disorganization, hallucinatory behavior, suspiciousness/persecution, hostility, uncooperativeness, and poor impulse control); no significant tolerability issue (investigator judged)
BRX[2]	12 weeks continuous	Outpatient status; PANSS total score≤70; score of ≤4 on each of the 4 PANSS items (conceptual disorganization, suspiciousness, hallucinatory behavior, and unusual thought content); CGI-S≤4; no current suicidal behavior as assessed by C-SSRS; no violent or aggressive behavior resulting in injury or property damage
QTP XR[3]	Meet at week 8/16	On established dose; CGI-S≤4; PANSS total score≤60 at week 0 (enrollment; inclusion criteria), with no change ≥10 points in PANSS total score from week 0 to 8 and from 0 weeks to 0 (randomization baseline)
OLZ[4]	8 weeks continuous	Did not meet relapse criteria (an increase in any BPRS positive item to >4, and either an absolute increase of ≥2 on that specific item or an absolute increase of ≥4 on the BPRS positive subscale [conceptual disorganization, hallucinatory behavior, suspiciousness, unusual thought content]; hospitalization due to positive psychotic symptoms; a priori secondary definition of relapse was a completed suicide or a serious suicide attempt [as determined by the investigator])
LUR[5]	12 weeks continuous	On a stable dose for 4 weeks prior to randomization; PANSS total score≤70, with PANSS item scores≤4 on all positive subscale items and "uncooperativeness" item, and a CGI-S<4. Note: two excursions (defined as 70<PANSS total score≤80 and/or a CGI-S=4 and/or PANSS positive subscale item=5) were permitted (post-stability attainment), except during the last 4 weeks of stabilization phase.
ASN[6]	26 weeks continuous	Did not experience loss of stability (PANSS total score increase of ≥20% increase in PANSS total score or 12 pts from baseline), or met any exclusion criteria (PANSS total score>75, CGI-S>3, score≥4 on items [unusual thought content, conceptual disorganization, hallucinatory behavior, hostility, or uncooperativeness]), or ISST scores of 2 on items 7, 10, or 11
ILO[7]	12 weeks continuous	On stable dose for at least 4 weeks prior to randomization; CGI-S≤4, five individual PANSS positive symptoms (delusions, conceptual disorganization, hallucinatory behavior, suspiciousness/persecution, hostility) and uncooperative item score≤4, PANSS total score ≤70, and not requiring any new acute treatment service intervention
PAL ER[8]	Meet at week 7/8 and 9–14[a]	Stable dosage regimen; PANSS total score≤70; CGI-S≤4; scores≤4 for PANSS items for delusions, conceptual organization, hallucinatory behavior, suspiciousness/persecution, hostility, and uncooperativeness.

Notes: [a]Obtained from https://clinicaltrials.gov/ct2/show/NCT00086320.
Abbreviations: ASE, asenapine; BPRS, Brief Psychiatric Rating Scale; BRX, brexpiprazole; CAR, cariprazine; CGI-S, Clinical Global Impression Scale – Severity; C-SSRS, Columbia-Suicide Severity Rating Scale; ER or XR, extended release; ILO, iloperidone; ISST, InterSePT Scale for Suicidal Thinking; LUR, lurasidone; OLZ, olanzapine; PAL, paliperidone; PANSS, Positive and Negative Syndrome Scale; PBO, placebo; QTP, quetiapine.
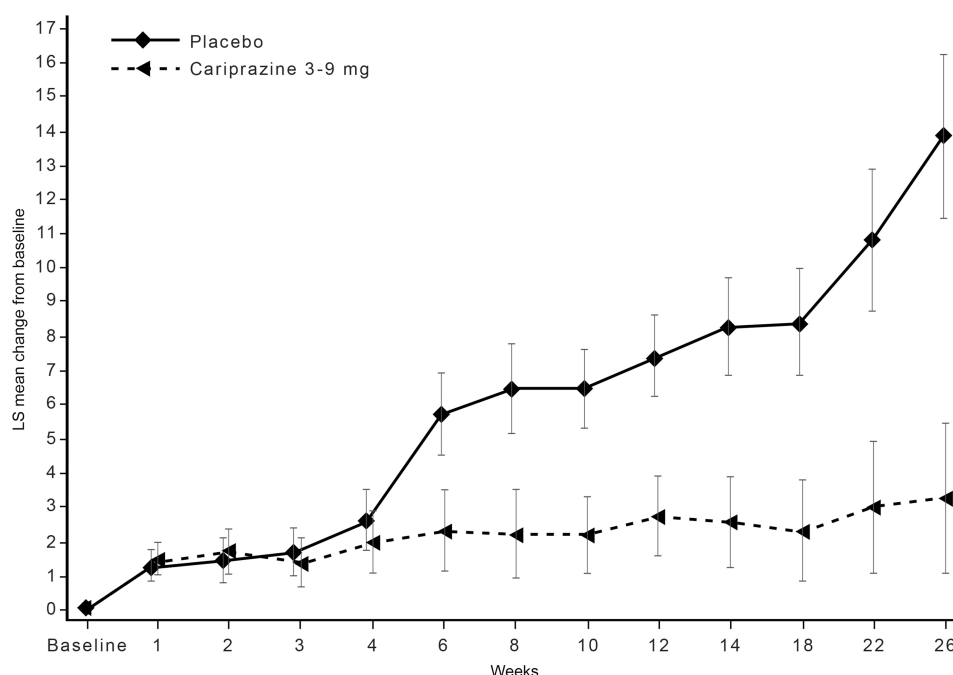
Figure S1 By-week change from baseline in PANSS total score (MMRM).
Abbreviations: LS, least squares; MMRM, mixed-effects model for repeated measures; PANSS, Positive and Negative Syndrome Scale.

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