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Relationship between antipsychotic blood levels and treatment failure during the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study

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ABSTRACT

Objective: Antipsychotic blood levels (ABLs) may help identify patients at risk for treatment failure. Reference ranges (RR) for plasma concentrations of ABLs that account for between-patient variability were developed for risperidone and olanzapine based on population pharmacokinetic models. The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) collected clinical outcomes and ABLs, allowing testing of the relationship of ABLs with outcomes.

Methods: ABLs from 694 patients who were randomized to olanzapine or risperidone were compared to the 80% RRs and were assessed as below or within/above the RR. Treatment failure was defined per any of these criteria: (1) emergency room visit for psychiatric reasons, (2) hospitalization for psychiatric reasons, (3) adverse event of completed suicide, suicidal ideation, or suicide attempt, (4) assaultive behavior, (5) arrested or jailed, (6) 2-point increase from baseline in Clinical Global Impression-Severity score, (7) 25% increase in Positive and Negative Syndrome Scale total score. Patients assessed with treatment failure within 100 days of drug concentration measurement were analyzed.

Results: Treatment failure occurred in 126 of 323 patients. The proportion of patients with ABLs below RR was 18.3% (59/323) compared to 10% expected in a fully adherent population. Among the 59 with ABLs below RR, 50.8% had treatment failure (compared to 36.4% for the 264 with ABLs within/above RR). The difference between groups was significant (odds ratio = 1.810; 95% CI = 1.025, 3.197; $p = 0.0408$).

Conclusions: Analysis of CATIE data showed that ABLs within the context of RRs may identify patients with higher risk of relapse.

1. Introduction

Schizophrenia, a severe psychiatric disorder, affects >21 million people worldwide (World Health Organization, 2017). The disorder is characterized by cognitive impairment as well as positive and negative symptoms, usually requiring lifelong treatment.

The majority of patients with schizophrenia will be at least partially non-adherent during their treatment (Byerly et al., 2007; Marder, 2013). Non-adherence, a primary factor in disease relapse, also incurs high health care and societal costs (Acosta et al., 2012; Novick et al., 2010). Even partial non-adherence increases risk of relapse (Weiden et al., 2004).

A retrospective review using a strict set of study inclusion criteria found mean nonadherence rates between 41.2% and 49.5% (Lacro et al., 2002). Valenstein et al. assessed approximately 34,000 Veterans Affairs patients with schizophrenia for 4 consecutive years. The cross-sectional prevalence of poor adherence was stable over time, with about 37% being poorly adherent each year, and 61% of patients had poor adherence at some point over 4 years (Valenstein et al., 2006). Methods to assess adherence such as clinician ratings, pill counts, patient reports, prescription renewal, urine/blood levels, and electronic monitoring have limited ability to detect antipsychotic non-adherence (Acosta et al., 2012; Byerly et al., 2005; Kane et al., 2013; Velligan et al., 2009).

Antipsychotic blood levels (ABLs) can be used as an approach to improve the reliability of adherence assessment, with the understanding that they may only reflect recent adherence behavior, as well as rapid elimination of the drug and treatment resistance (Hiemke et al., 2011; Horvitz-Lennon et al., 2017; Howes et al., 2017). A recently developed method of "reference ranges" (RRs) for risperidone and olanzapine was used in this study to better interpret plasma concentrations of

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ABLs (Korell et al., 2018; Korell et al., 2017). The RRs are based on population pharmacokinetic models of fully adherent patients, and account for between- and within-patient variability for a given dose and time after dose. Use of RRs for assessment of ABLs may provide a reliable indication of treatment adherence (Green et al., 2017; Korell et al., 2017).

The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study, designed to compare the effectiveness of atypical and conventional antipsychotic drugs, collected clinical outcomes and ABLs (Lieberman et al., 2005). The purpose of this study was to assess the relationship between the incidence of treatment failure and ABLs within the context of RRs in patients with schizophrenia using data from the CATIE trial.

2. Methods

Methods for the conduct of the CATIE trial have been previously described (Lieberman et al., 2005). Briefly, a total of 1493 patients with schizophrenia were randomized to perphenazine, olanzapine, quetiapine, risperidone or ziprasidone for up to 18 months of treatment. The CATIE protocol included obtaining random blood samples to measure antipsychotic levels. The limited access data sets distributed from the CATIE trial provided ABLs from 694 patients who were randomized to either olanzapine or risperidone.

Patients were identified as treatment failures based on presence of any of the following criteria: (1) emergency room visit for psychiatric reasons, (2) hospitalization for psychiatric reason, (3) adverse event of completed suicide, suicidal ideation, or suicide attempt, (4) assaultive behavior, (5) being arrested or jailed, (6) 2-point increase from baseline in the Clinical Global Impression-Severity (CGI-S) score, (7) 25% increase in the Positive and Negative Syndrome Scale (PANSS) total score (Table 1). The clinical outcomes in CATIE were reviewed and these criteria were selected as most relevant for poor clinical outcome based on significant negative behavior or meaningful change in a rating scale, i.e., a 25% increase in PANSS (Csernansky et al., 2002).

2.1. Development of reference ranges

Eighty percent population RRs were developed and evaluated for risperidone and olanzapine, based on oral formulation data (Korell et al., 2018; Korell et al., 2017). Population pharmacokinetic (pop-PK) models were developed using plasma concentrations data from patients with observed medication intake during phase 2 and 3 registration trials, and were internally validated by the sponsors of each antipsychotic agent (risperidone, Janssen Research & Development, Raritan, NJ; olanzapine, Eli Lilly and Company, Indianapolis, IN).

A database of patients and their demographic characteristics was constructed from patients who participated in 25 clinical trials during development of Janssen's antipsychotics. The characteristics and covariates from this database were used to simulate expected concentrations, assuming perfect compliance with the prescribed treatment regimen described above. The simulated concentrations were sorted into 80% population RRs for the test analytes. Plasma concentrations for 80% of the fully adherent patient population are represented by the range between the lower 10% and upper 90% boundaries (Table 2). In other words, even in fully adherent subjects, 10% of subjects will be below and above the RR.

Table 1
Treatment failure criteria.

1. Use of emergency room for psychiatric reasons
2. Hospitalization for psychiatric reasons
3. Adverse event (completed suicide, depression suicidal, suicidal ideation, suicide attempt)
4. Assaultive behavior such as violent/non-violent crime, violence
5. Arrested, or spent nights in jail
6. 2-point increase from baseline in Clinical Global Impression-Severity score
7. 25% increase in Positive and Negative Syndrome Scale total score

Table 2
Reference ranges for once-daily dosing of risperidone and olanzapine.

Average concentration[a] (ng/mL)										
Time Since Last Dose:	0 to 4 h		4 to 9 h		9 to 14 h		14 to 20 h		20 to 24 h	
Percentile:	≤10	≥90	≤10	≥90	≤10	≥90	≤10	≥90	≤10	≥90
Risperidone										
1 mg	5.33	22.1	5.57	21.7	4.50	18.2	3.55	15.3	2.86	13.1
2 mg	10.7	44.2	11.1	43.5	9.01	36.4	7.10	30.6	5.72	26.2
3 mg	16.0	66.3	16.7	65.2	13.5	54.7	10.6	45.8	8.58	39.3
4 mg	21.3	88.4	22.3	87.0	18.0	72.9	14.2	61.1	11.4	52.5
5 mg	25.6	104	27.4	106	22.5	89.9	17.7	75.9	14.3	65.3
6 mg	32.0	133	33.4	130	27.0	109	21.3	91.7	17.2	78.7
8 mg	42.6	177	44.6	174	36.0	146	28.4	122	22.9	105
Olanzapine										
2.5 mg	3.75	11.2	4.05	11.9	3.50	10.7	2.78	9.86	2.16	9.25
5 mg	7.50	22.4	8.10	23.7	7.00	21.4	5.56	19.7	4.32	18.5
7.5 mg	11.2	33.6	12.2	35.6	10.5	32.1	8.35	29.6	6.49	27.7
10 mg	15.0	44.7	16.2	47.4	14.0	42.8	11.1	39.4	8.65	37.0
15 mg	22.5	67.1	24.3	71.1	21.0	64.3	16.7	59.2	13.0	55.5
20 mg	30.0	89.5	32.4	94.9	28.0	85.7	22.3	78.9	17.3	74.0

h = hours.
[a] Concentrations represent active moiety for risperidone and parent molecule for olanzapine.

The RRs were time-binned to account for the change in plasma concentrations as a function of time after a dose. The 80% RRs were generated, taking into account the terms representing variability between patients and within patients (i.e., residual variability) from the pop-PK models. The 80% RRs were evaluated externally, using new sets of studies, which were different from the studies used to build the pop-PK models. For both risperidone and olanzapine, the RRs are available for the most commonly used marketed doses, and for both once-daily and twice-daily regimens (Korell et al., 2017; Korell et al., 2018).

2.2. Assessment

Drug concentrations were measured every three months in the CATIE study. Although the visits were 90 days apart, we added in 10 additional days in selecting the patients. Only those patients who had an assessment of treatment failure within 100 days from the visit where the drug concentrations were measured were included in the evaluation. To make a prudent association between the drug concentration levels and the treatment failure status, patients who skipped the visit after the blood draw, those who discontinued from the study after blood draw, or those who did not adhere to the study visit schedule had to be excluded from the analysis as inclusion of the data from these patients would have made our analysis less sensitive to drug concentration levels. Treatment failure status within the 100-day window was mapped to the drug concentration flag at the previous visit. For patients who were treatment failures at multiple visits, their first occurrence of treatment failure and its corresponding drug concentration flag at the previous visit was used for the analysis.

Distribution of ABL categories in the treatment failure group was compared to the distribution in the non-treatment failure group. Odds ratio (OR) (95% CI) of incidence rate of treatment failure in the below range group vs within/above range group was estimated.

Patients who were randomized to olanzapine or risperidone during phases 1/1B/2 and had drug concentration data within the dosing intervals for which RRs were available, were compared to the 80% RRs and were assessed as below or within/above the RR. Patients were counted separately for each treatment (i.e., olanzapine or risperidone) in determining treatment failure and in assessing whether they were below or within/above the RR. However, they were counted once in the assessment of demographic summaries.

Several definitions of treatment failure were evaluated depending on the individual criteria that were considered in the definition (Table 3).

3. Results

Out of the 694 patients who had ABLs, a total of 316 patients were included in the analysis of treatment failure (Table 4). There were 7 patients who were on risperidone as well as olanzapine. When we assessed treatment failure rates in relation to drug levels, we counted these patients twice – once for olanzapine and once for risperidone. These patients were categorized as below or within/above reference range separately for each medication. The number of patients receiving risperidone was 139 (44.0%), and the number of patients receiving olanzapine was 184 (58.2%). Therefore, the total for the All category was 323. The number of patients used in the analysis of treatment failure in each group varied depending on the definition. Fig. 1 shows the incidence of treatment failure based on the drug concentration being below the RR or within/above the RR, in specified categories of treatment failure criteria. The majority of categories show a lower percentage of treatment failure with drug concentrations within/above the RR as compared to below the RR.

In the All Criteria category, treatment failure occurred in 39.0% (126/323) of the patients. The proportion of patients who had drug concentration below the RR was 18.3% (59/323). Out of the 59 patients with ABLs below range, 30 (50.8%) had treatment failure compared to 96 (36.4%) out of 264 patients with levels within/above range who had treatment failure. The difference between the two drug concentration groups was significant (OR [95% CI]: 1.810 [1.025, 3.197]; $p = 0.0408$).

In the definition that excluded assaultive behavior or jail (Clinical), treatment failure occurred in 32.7% (106/324) of the patients. The proportion of treatment failures in the below range group was 44.1% (26/59) compared to 30.2% (80/265) in the within/above range group (OR [95% CI]: 1.822 [1.023, 3.245]; $p = 0.0416$). In the definition of treatment failure which did not include the PANSS (No PANSS) treatment failure occurred in 26.7% (93/348) of the patients. The proportion of treatment failures in the below range group was 39.7% (23/58) compared to 24.1% (70/290) in the within/above range group (OR [95% CI]: 2.065 [1.144, 3.729]; $p = 0.0161$). Criteria were met for treatment failure due to a 2-point increase from baseline in CGI-S scores (CGI-S) in 6.2% (23/373) of the patients. The proportion of treatment failure in the below range group was 14.8% (9/61) compared to 4.5% (14/312) in the within/above range group (OR [95% CI]: 3.684 [1.516, 8.950]; $p = 0.0040$). Criteria for treatment failure were met due to hospitalization or emergency room visit for psychiatric reasons (Hosp/ER) in 13.2% (46/348) of the patients. The proportion of treatment failures in the below range group was 17.9% (10/56) compared to 12.3% (36/292) in the within/above range group (OR [95% CI]: 1.546 [0.717, 3.331]; $p = 0.2661$). Treatment failure rate by drug concentration category below the RR vs within/above the RR was significant ($p < 0.05$) for All, Clinical, Scales, CGI-S, combined category of Legal/CGI-S, No PANSS, and combined category of No PANSS/No Hosp categories (Fig. 2).

Table 4
Demographics and baseline characteristics ($N = 316$).

Age, years, n (%)	
18–25	38 (12.0)
26–50	220 (69.6)
51–64	57 (18.0)
>64	1 (0.3)
Mean (SD)	40.9 (11)
Median (range)	43 (18; 67)
Race, n (%)	
American Indian/Alaska Native	3 (0.9)
Asian	11 (3.5)
Black or African American	98 (31.0)
Hawaiian or Pacific Islander	1 (0.3)
More than one race	2 (0.6)
White	201 (63.6)
Sex, n (%)	
Male	227 (71.8)
Female	89 (28.2)
Treatment, n (%)[a]	
Risperidone	139 (44.0)
Olanzapine	184 (58.2)

n = number, SD = standard deviation.
[a] 7 patients were on risperidone as well as olanzapine in two different phases.

4. Discussion

Analysis of the CATIE data showed significantly higher relapse rates were observed in patients with ABLs below RRs compared to ABLs within/above RRs (OR [95% CI]: 1.810 [1.025, 3.197]; $p = 0.0408$).

Criteria grouped into categories of treatment failure frequency and rate by drug concentration were assessed within categories. The proportion of treatment failures with ABLs below range was higher than the proportion of ABLs within/above range in most categories, although the difference between rate of treatment failures and ranges were significant in only about half of the categories.

Although definitive conclusions cannot be made regarding the influence of each category on the proportion of treatment failures for ABLs below range compared to ABLs within/above range, categories with significantly more treatment failures with ABLs below range than with ABLs within/above range included All criteria ($p = 0.0408$), Clinical (all criteria except assaultive behavior or jail) ($p = 0.0416$), and Scales (a 2-point increase from baseline in CGI-S score, and a 25% increase in PANSS total score) ($p = 0.0251$). The PANSS category had a higher

Table 3
Specified groups of treatment failure criteria.

Criteria	All $n = 323$	Clinical $n = 324$	Legal $n = 384$	Scales $n = 356$	PANSS $n = 354$	CGI-S $n = 373$	Legal/CGI-S $n = 382$	AE/Hosp/ER $n = 348$	AE/ER =373	Hosp/ER n = 348	No Hosp $n = 357$	No PANSS n = 348	No PANSS/No Hosp $n = 380$	AE n = 373
Use of emergency room for psychiatric reasons	x	x						x	x	x	x	x	x	
Hospitalization for psychiatric reasons	x	x						x		x		x		
Adverse event (completed suicide, depression suicidal, suicidal ideation, suicide attempt)	x	x						x	x		x	x	x	x
Assaultive behavior (violent/non-violent crime, violence)	x		x				x				x	x	x	
Arrested, or spent nights in jail	x		x				x				x	x	x	
2-point increase from baseline in CGI-S score	x	x		x		x	x				x	x	x	
25% increase in PANSS total score	x	x		x	x						x			

AE = adverse event, CGI-S = Clinical Global Impression-Severity, ER = emergency room, Hosp = hospitalization, PANSS = Positive and Negative Syndrome Scale.

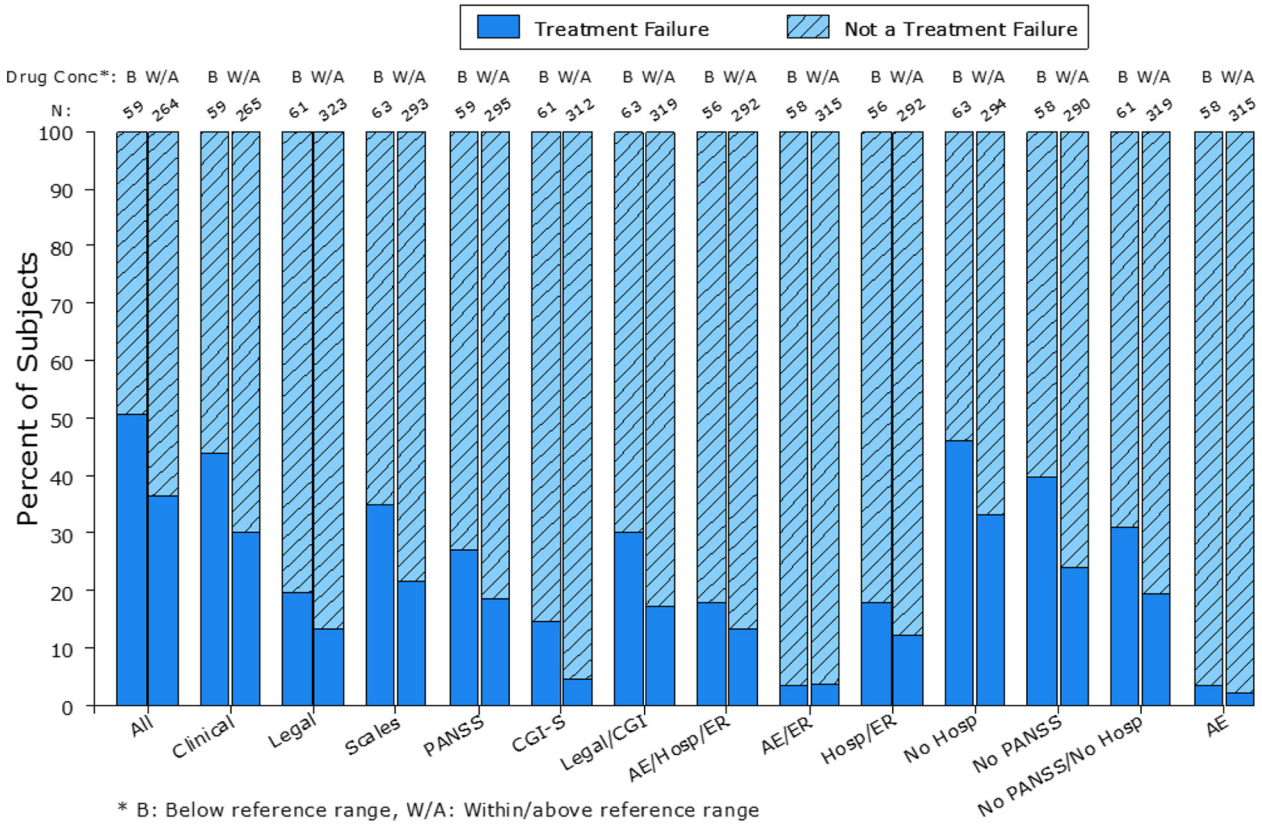

Fig. 1. Frequency distribution of treatment failure status by drug concentration category. Abbreviations: AE = adverse event, B = below reference range, CGI-S = Clinical Global Impression-Severity, conc = concentration, ER = emergency room, hosp = hospitalization, PANSS = Positive and Negative Syndrome Scale, W/A = within/above reference range.

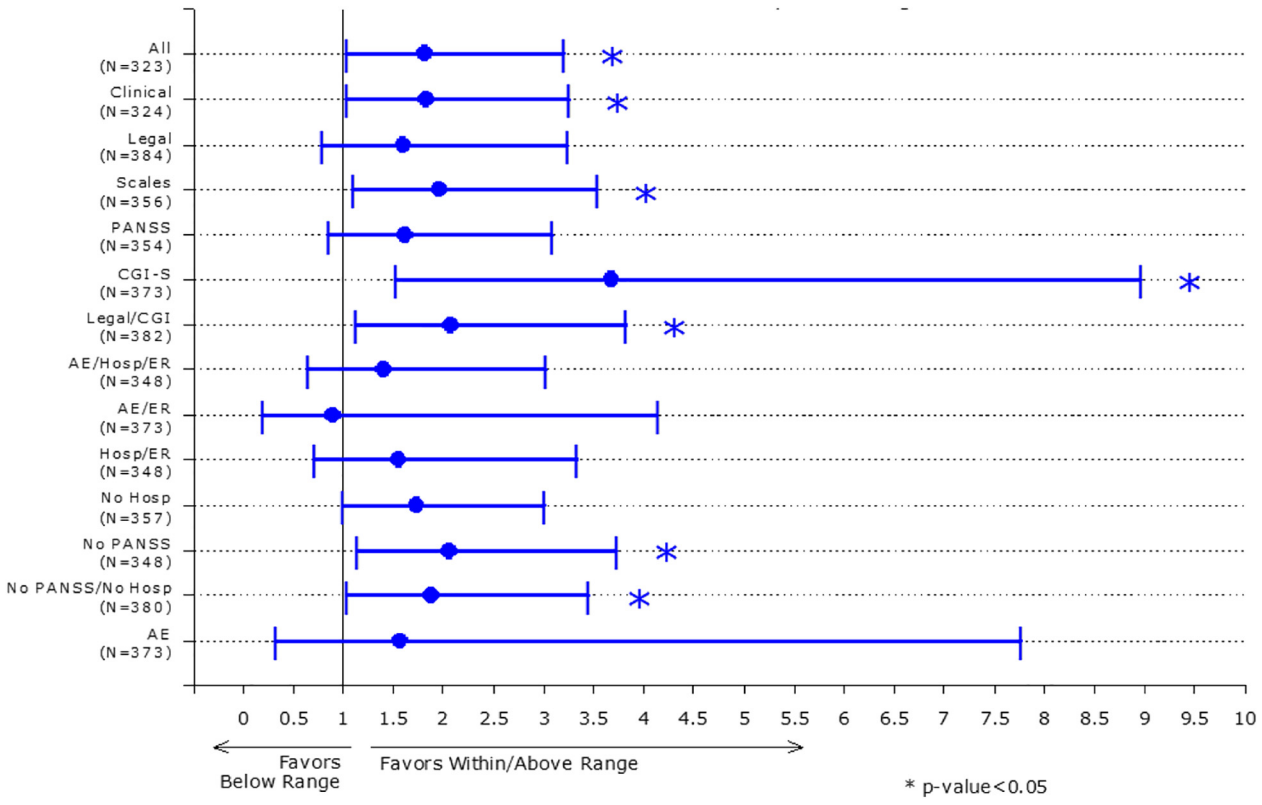

Fig. 2. Treatment failure rate by drug concentration category – below reference range vs within/above reference range (odds ratio [95% CI]). Abbreviations: AE = adverse event, CGI-S = Clinical Global Impression-Severity, ER = emergency room, hosp = hospitalization, PANSS = Positive and Negative Syndrome Scale.

proportion of treatment failures (20.1% [71/354]) than the CGI-S category (6.2% [23/373]), however, the treatment failure rate in the CGI-S category was significantly higher in ABLs below range than ABLs within/above range ($p = 0.0040$) than in the PANSS category ($p = 0.1404$). Some of the definitions of treatment failure appeared to be more sensitive to the drug levels with regards to treatment failure as seen in the categories of No PANSS, Legal/CGI (combined category), CGI-S and Scales compared to the others.

Using the RRs, ABLs can be checked for consistency with what is expected for a given formulation, dose, and time after dose. Perfect adherence was assumed when defining the RRs. Due to naturally occurring variation, 10% of patients are expected below-RR ABLs despite perfect adherence. It is therefore not surprising to find that >10% (in this case 18%) of patients from the CATIE evaluation dataset had below-RR ABLs, since the occurrence of partial- or non-adherence is expected even within controlled trials (especially when oral medications are used). Considering that this was a well-controlled trial with pill counts, it would be expected that in a clinical population an even higher percentage would be below the RR but this would need to be tested in a more naturalistic setting. It should be noted that the system can be misled by taking the medication shortly before the measurement takes place, and levels could then be in range even if patients were non-adherent the previous days. Therefore, 10% is not an absolute cut-off. The findings of the present analysis of CATIE data suggest ABLs may function as a potential risk factor for treatment failure but would be insufficiently sensitive or specific to reliably predict treatment failure on their own. Consequently, ABLs need to be combined with clinical evaluation of the patient. When a patient experiences a treatment failure, it is often difficult to determine if the cause is lack of adherence, lack of efficacy of the medication, or a drug interaction that reduces the efficacy of the antipsychotic. In cases with low ABLs, treatment failure is often a result of sustained concentrations below the RR, which can result from lack of adherence or unaccounted drug-drug interactions. Smoking and CYP2D6 metabolizer status were included as covariates in the POP-PK models used to generate the 80% reference ranges. Therefore, the reference ranges also reflect variability due to these covariates. Nevertheless, smoking and rapid metabolizer status will increase the probability for detecting concentrations below the 80% RR for olanzapine and risperidone, respectively.

Our study reports the use of RRs in a retrospective analysis of ABLs and incidence of treatment failure from the CATIE trial. The use of ABLs with RRs and treatment failure would need to be characterized further in clinical trials, as well as used with other antipsychotics. Plasma concentration RRs for oral aripiprazole, paliperidone, and quetiapine have also been developed (Korell et al., 2018; Korell et al., 2017).

ABLs within the context of RRs can potentially identify patients with higher risk of treatment failure. With the use of ABLs in relation to RRs, the clinician may gain confidence in better assessing treatment adherence in some patients and potentially intervene prior to a full treatment failure. These results could be used to direct appropriate treatment.

Authorship contributions.

Participated in study design: RM, AS, AV, BR, AS

Performed data analysis: RM.

Drafted or revised the manuscript: RM, AS, AV, BR, AS.

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Conflicts of interest

The authors are employees of Janssen Research & Development, LLC and potentially hold stock and/or stock options in the company.

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