



Introduction

Treatment guidelines, clinical support tools, and expert consensus guidelines recommend measurement of antipsychotic blood levels, as adherence to antipsychotic therapy is critical to positive treatment outcomes.¹⁻⁶ There is a compelling clinical need for antipsychotic drug blood levels. Clinicians lack quantitative insight into antipsychotic treatment failures. The utility of current testing methods is limited because of the required turnaround time. When it takes days to receive a blood level, there is no possibility for immediate personalized/tailored dosing, rapid medication adjustments, patient triage, care and disposition.⁷

POCT provides immediate, objective drug level results during the patient visit, so clinicians can provide personalized treatment plans to combat problems such as nonadherence, pharmacokinetic interactions (drug-drug, changes in lifestyle), poor response, or unacceptable toxicity. The aims of the study were to validate a whole blood (WB) POCT assay for clozapine (CLZ), and to develop WB POCT assays for total aripiprazole (aripiprazole + major metabolite dehydroaripiprazole; ARI), and total risperidone (risperidone + major metabolite 9-hydroxyrisperidone; RSP).

Methods

Automated homogenous immunoassays (MyCare[™] Psychiatry assay kits for Clozapine (FDA Allowed/CE Mark), Total Aripiprazole (CE Mark), and Total Risperidone (CE Mark)) used to measure clozapine, aripiprazole, and risperidone, respectively, were modified to test analyte levels using capillary blood from a finger stick. Assay kits consist of two reagents. Formulation changes were made in reagent one to ensure lysing of the red blood cells in whole blood and compensate for matrix, while still maintaining reagent stability. The antibody reagent was minimally modified to retain the specificity for the target with minimal cross-reactivity for other antipsychotics. The POCT analyser, the MyCare Insite, is a small, portable analyser used for rapid results (in about 8 minutes). The analyser uses a stored calibration curve that is valid for the shelf-life of the reagent. Analytical performance of MyCare Insite Clozapine Test (CLZ-POCT) was evaluated according to CLSI guidelines with 3 reagent lots, while ARI-POCT and RSP-POCT were evaluated using scaled-up reagents. Testing was performed on MyCare Insites using buffered controls and spiked WB samples and real patient samples for method comparisons.

Results

Table 1 shows that the linear measuring range of the assays covers the reference ranges recommended in practice guidelines.

Table 1

Assay	Linear Range ng/mL	Recommended Reference Range[ng/mL]
Clozapine	122 – 1390	350 – 600
Total Aripiprazole	120 – 1000	150 – 500
Total Risperidone	16 – 120	20 – 60

Table 2 shows the cross-reactivity of the risperidone antibody that detects total risperidone without interference from major metabolites, which appear at < 20% of the parent drug.

Table 2

Compound	Cross-Reactivity
9-hydroxyrisperidone	101%
7-hydroxyrisperidone	< 60%
N-desalkyl risperidone	< 5%

Table 3 shows the assay bias of the aripiprazole antibody that detects total aripiprazole without interference from major metabolites. Assay bias is measured in the presence of the interferent.

Table 3

Compound	Assay bias
3,4-dihydro-7-(3'carboxy) propoxy-2(1H) quinolinone (OPC-3373)	3%
1-(2,3-dichlorophenyl) piperazine (DCPP)	6%

Table 4 shows the cross-reactivity of the clozapine antibody that detects clozapine without interference from major metabolites or the related antipsychotic medication olanzapine.

Table 4

Compound	Cross-Reactivity
Clozapine-N-oxide	< 3%
Norclozapine	< 1%
Olanzapine	< 2%

Figure 1 shows POC analyser kinetics for risperidone without red blood cell lysis and after optimization of reagent 1 formulation for RBC lysis.

Figure 1

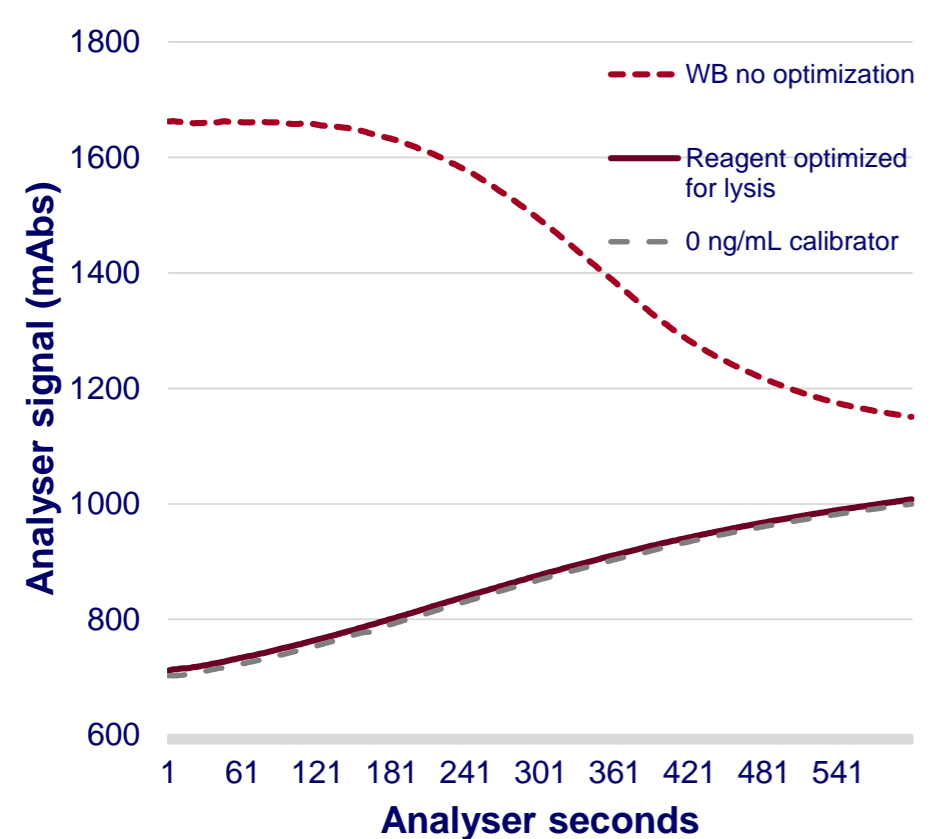


Figure 2 shows the six-point, non-linear calibration for the total risperidone test. The calibration is stored on a lot specific RFID card.

Figure 2

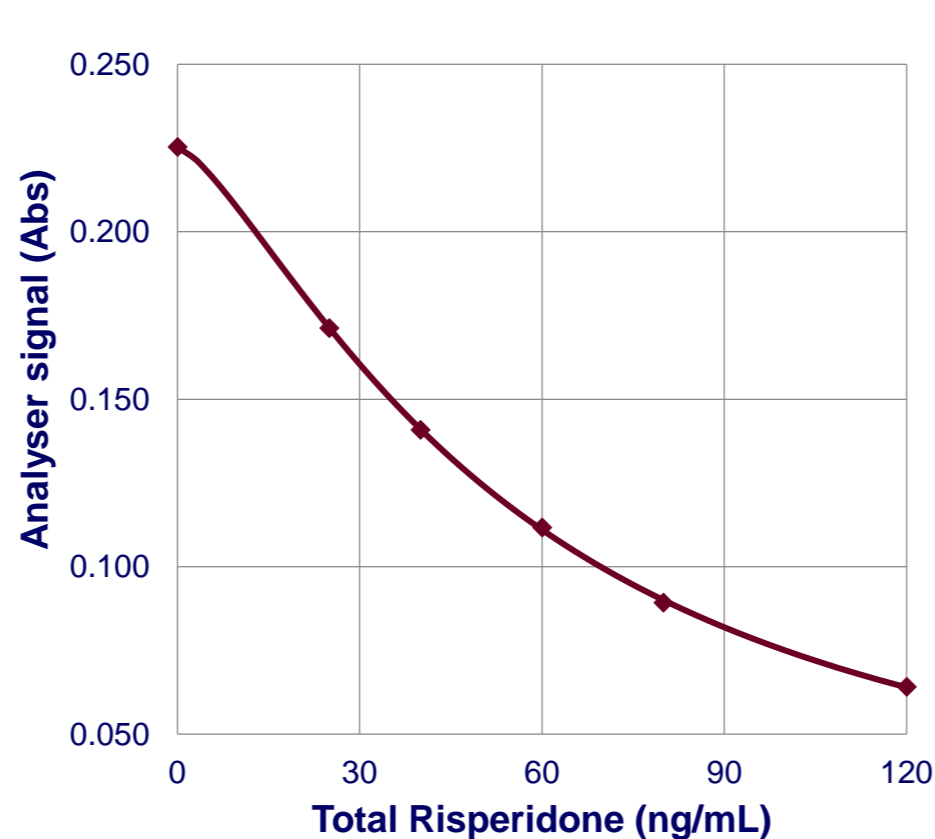


Figure 3 shows the linearity of the total aripiprazole test with spiked whole blood (n=4) samples. Percent deviation from linearity was <10% at all concentrations.

Figure 3

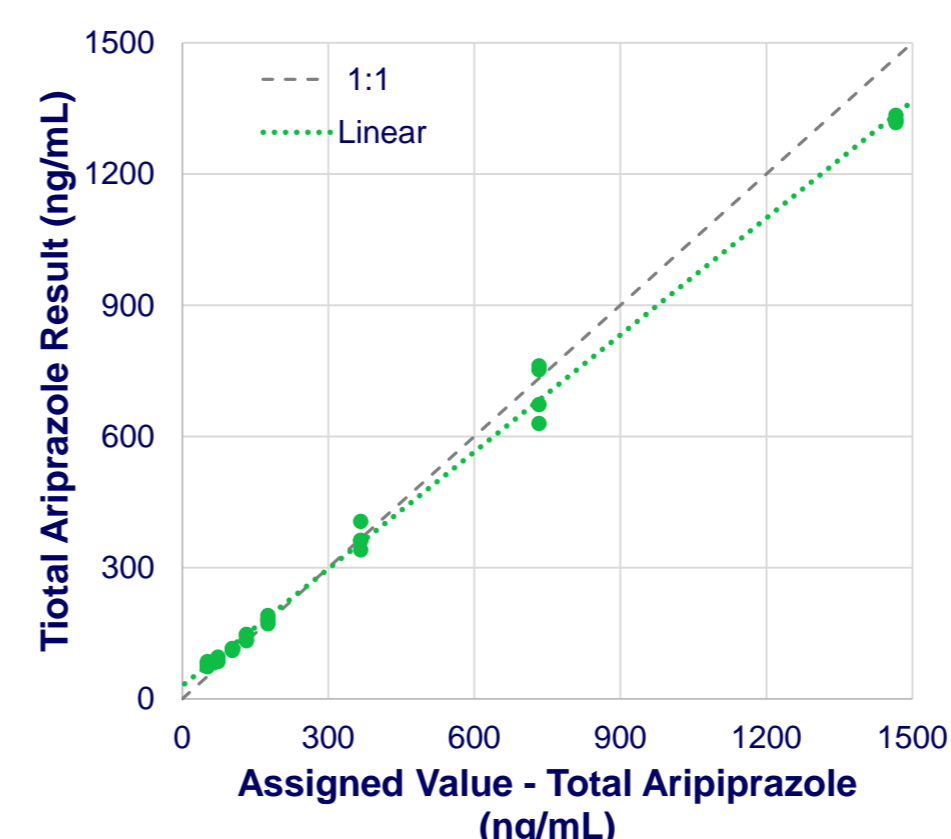


Figure 4 shows the linearity of the clozapine test. CLSI EP6 linearity was demonstrated with 10 levels from 122 to 1390 ng/mL, measured n = 5.

Figure 4

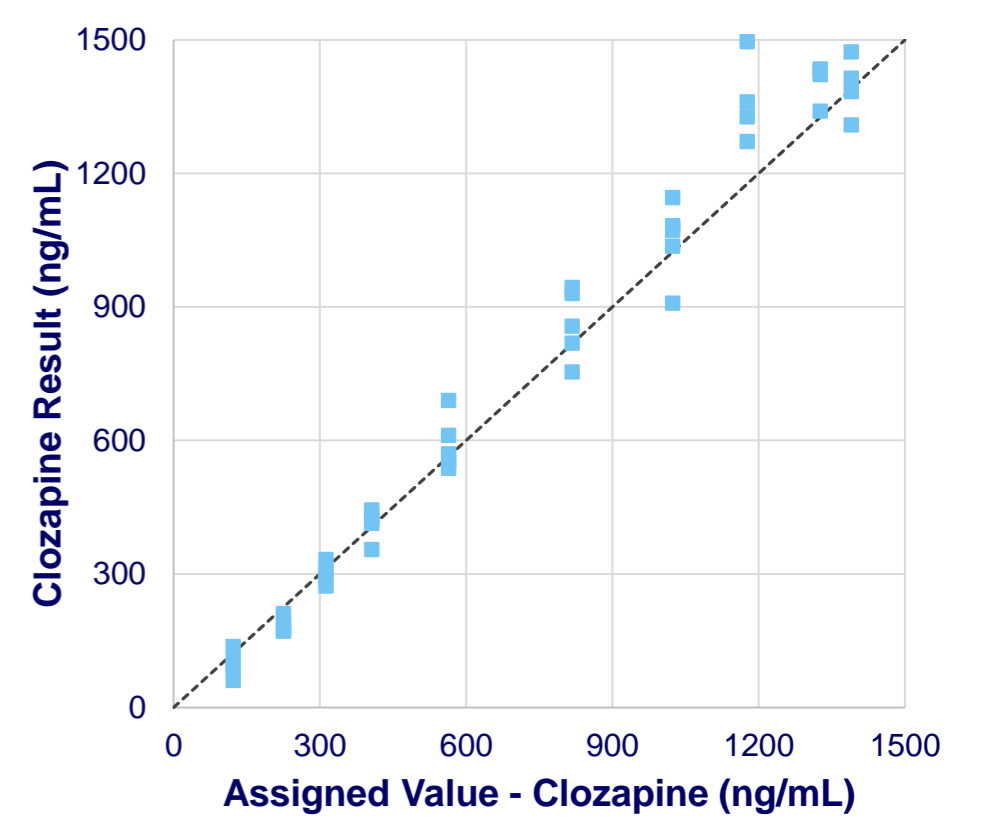


Figure 5 shows a method comparison for the Insite Total Aripiprazole test vs. LC-MS/MS. Equation of the line (Passing-Bablok) $y = 1.06x - 3.0$, $R = 0.958$, $n = 17$.

Figure 5

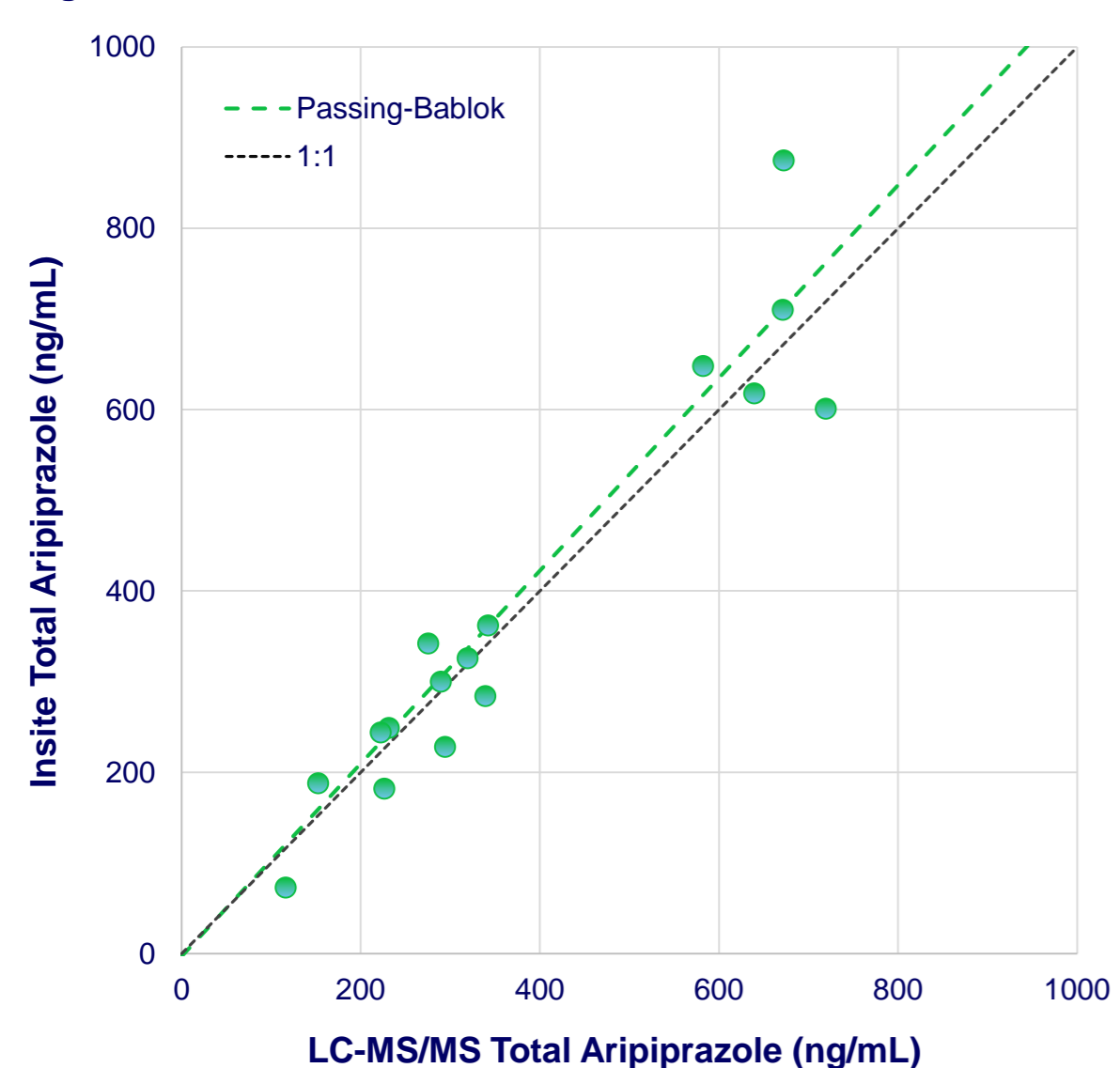


Figure 6 shows a method comparison for the Insite clozapine test vs. LC-MS/MS. Equation of the line (Passing-Bablok) $y = 0.971x - 21.2$, $R = 0.9$, $n = 304$.

Figure 6

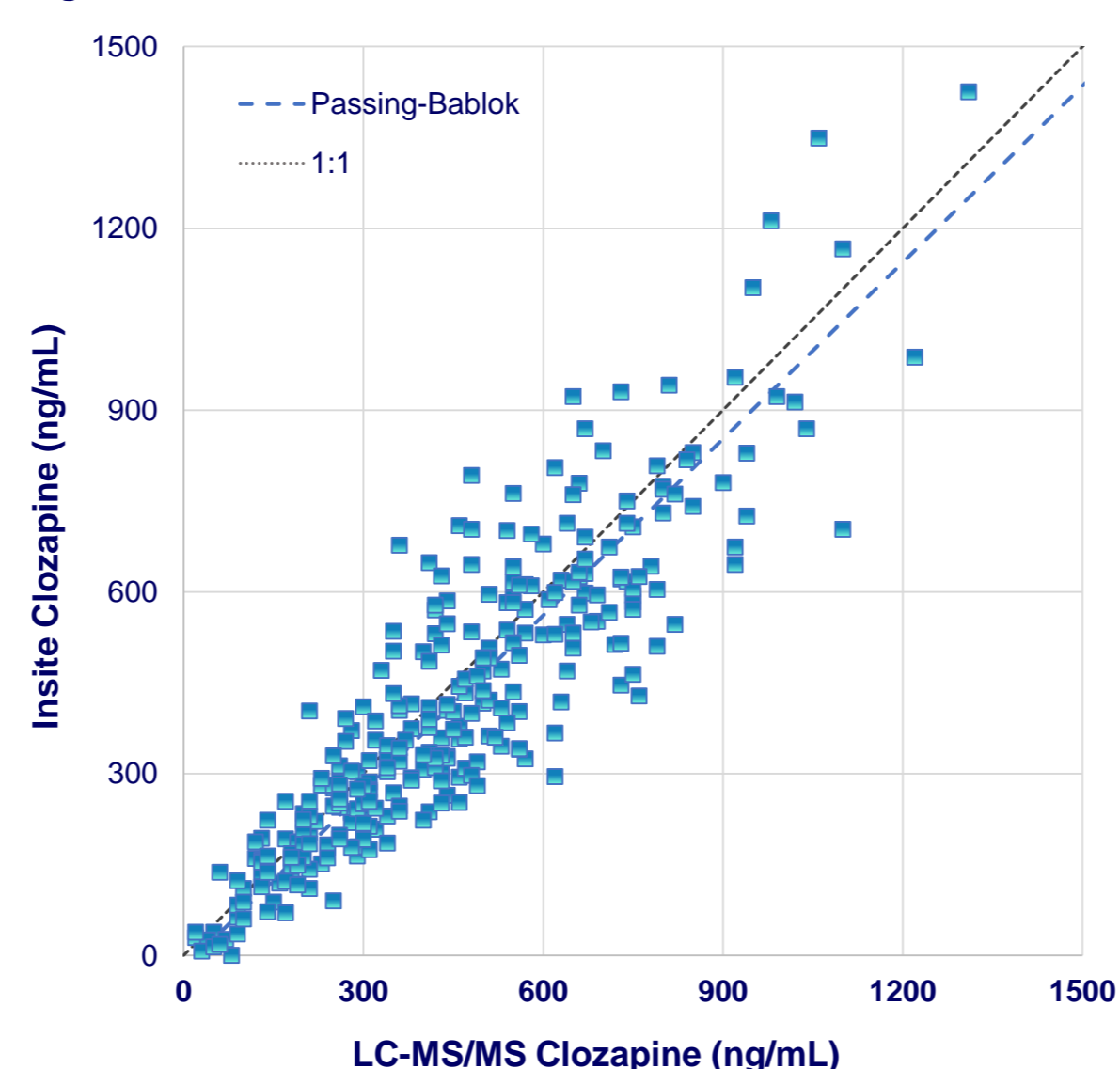


Figure 7 shows the total aripiprazole test imprecision with spiked whole blood samples at 8 concentrations. All CVs were < 10%.

Figure 7

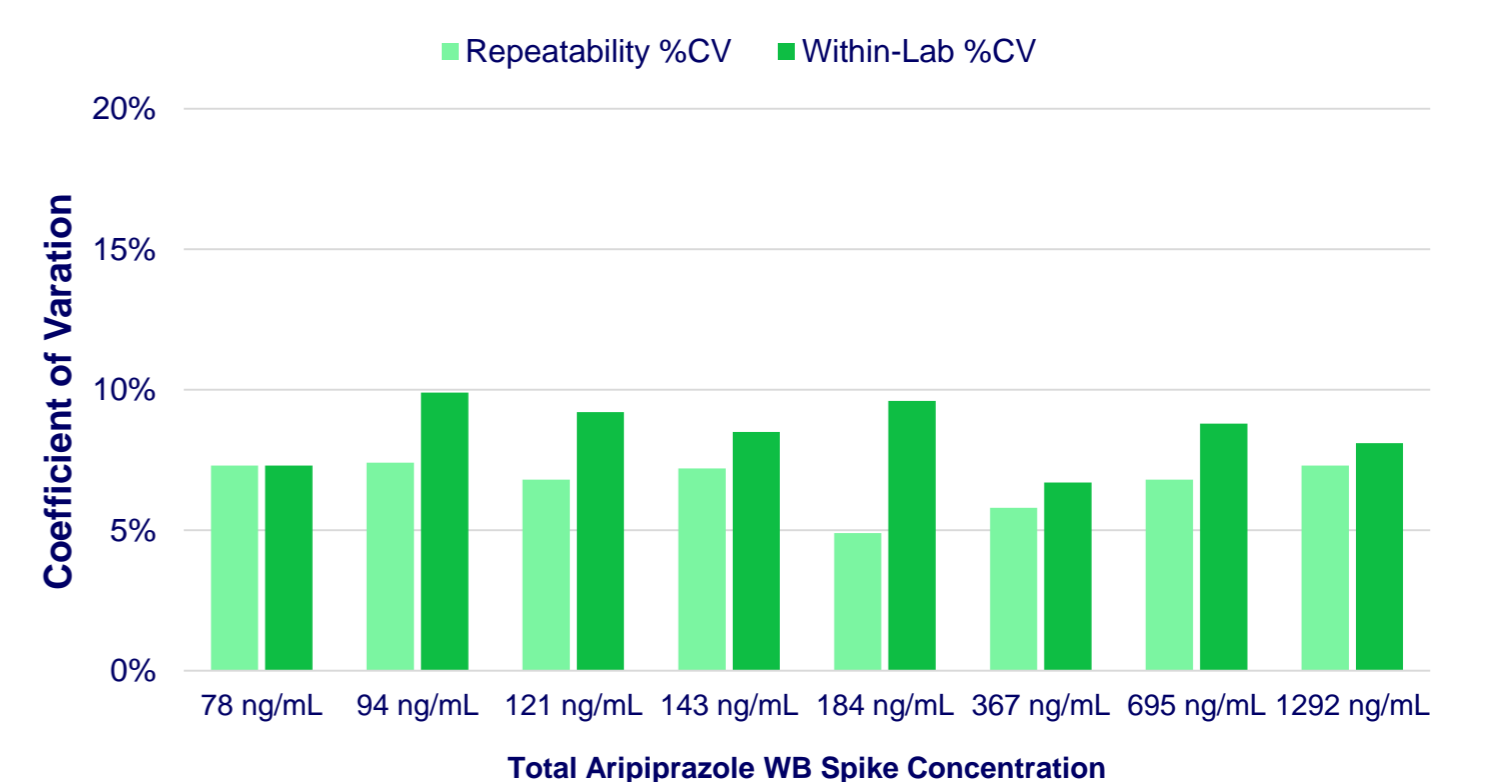
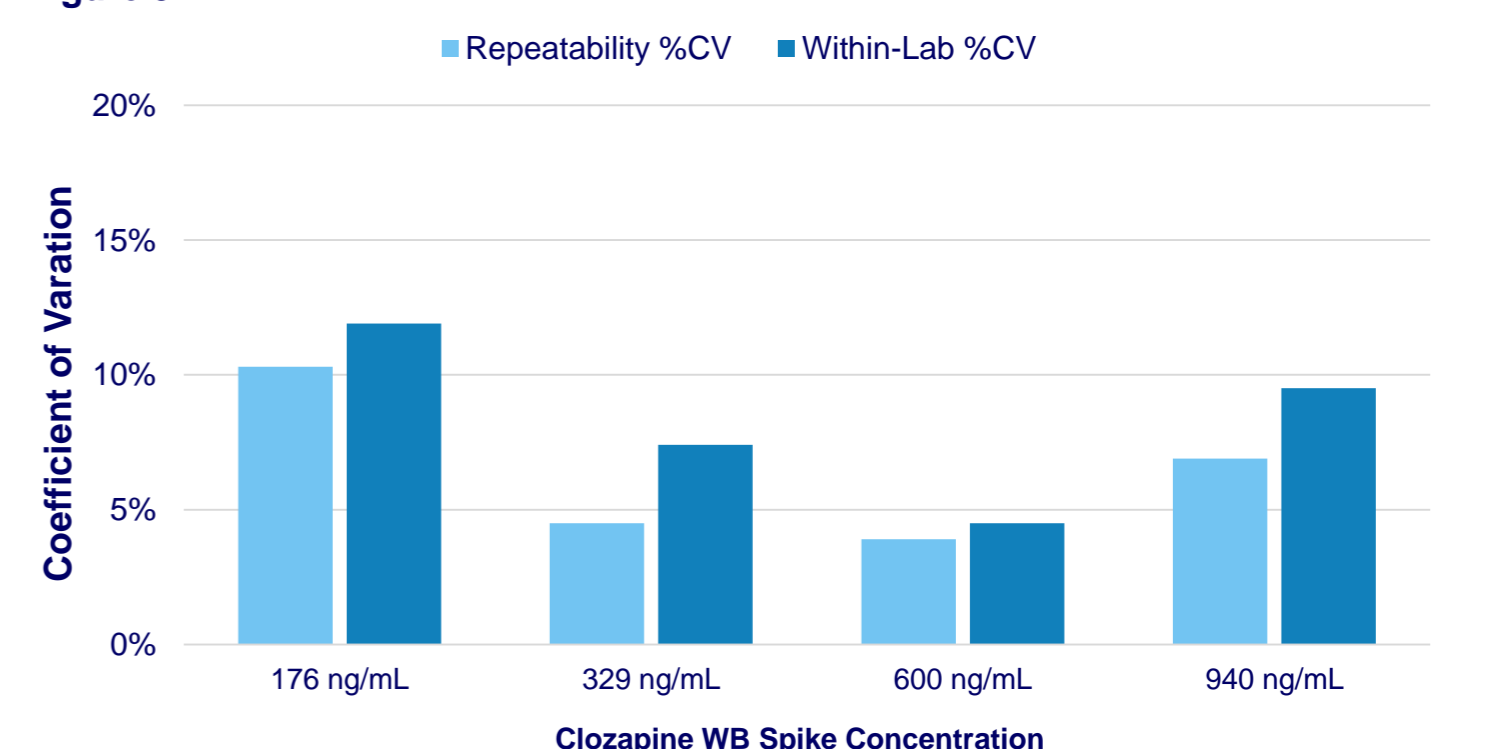


Figure 8 shows the clozapine test imprecision with spiked whole blood samples at 4 concentrations. All CVs were ≤ 12%.

Figure 8



Conclusions

- The first point of care tests have been developed to test blood levels of the antipsychotics clozapine, aripiprazole, and risperidone.
- Time to result is less than 8 minutes using a capillary blood sample from a fingerstick
- Compared to reference methods point of care results are precise and accurate.
- Point of care testing for antipsychotics fulfills an unmet medical need.

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