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# THE INFLUENCES OF ADHERENCE TO TAMOXIFEN AND CYP2D6 PHARMACOGENETICS ON PLASMA CONCENTRATIONS OF THE ACTIVE METABOLITE (Z)-ENDOXIFEN IN BREAST CANCER

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Tamoxifen efficacy in breast cancer is suspected to depend on adherence and intact drug metabolism. We evaluated the role of adherence behavior and pharmacogenetics on the formation rate of (Z)-endoxifen. In 192 Brazilian patients, we assessed plasma levels of tamoxifen and its metabolites at 3, 6, and 12 months of treatment (LC-MS/MS), adherence behavior (Morisky Medication Adherence Scale), and CYP2D6 and other pharmacogene polymorphisms (MALDI-TOF mass spectrometry and real-time PCR). Adherence explained 47% of the variability of tamoxifen plasma concentrations ( $p < 0.001$ ). While CYP2D6 alone explained 26.4%, the combination with adherence explained 40% of (Z)-endoxifen variability at 12 months ( $p < 0.001$ ). The influence of low adherence not to achieving relevant (Z)-endoxifen levels was the highest in patients with non-compromised CYP2D6 function (RR 3.65, 95%CI 1.48–8.99). As a proof-of-concept, we demonstrated that (Z)-endoxifen levels are influenced by patient adherence to both tamoxifen and CYP2D6, which is particularly relevant for patients with full CYP2D6 function.

**Keywords:** Tamoxifen; Breast Cancer; CYP2D6; Adherence; Endoxifen.