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Titel des Beitrags: Amitriptyline or not, that is the question: pharmacogenetic testing of CYP2D6 and CYP2C19 identifies patients with low or high risk for side effects in amitriptyline therapy.

Abstract: BACKGROUND: Amitriptyline has been replaced in many countries by alternative and more expensive drugs based on claims of improved tolerability and toxicity and despite slightly reduced efficacy. Preliminary studies indicate that adverse effects could be linked to polymorphisms of drug-metabolizing enzymes, but information on their clinical impact remains scanty and includes mainly case reports. We conducted a prospective blinded two-center study seeking correlations between CYP2C19 and CYP2D6 genotypes, drug concentrations, adverse events, and therapy response. METHODS: Fifty Caucasian inpatients with at least medium-grade depressive disorder received amitriptyline at a fixed dose of 75 mg twice a day. Blood samples for concentration monitoring of amitriptyline and nortriptyline were taken weekly until discharge along with evaluations of depression (Hamilton Depression Scale and Clinical Global Impression Scale) and side effect (Dosage Record and Treatment Emergent Symptoms Scale; DOTES) scores. RESULTS: In a ROC analysis, nortriptyline but not amitriptyline concentrations correlated with side effects (DOTES sum score>or=5; area under the curve, 0.733; P = 0.008). Carriers of two functional CYP2D6 alleles had a significantly lower risk of side effects than carriers of only one functional
allele (12.1% vs 76.5%; P = 0.00001). The lowest risk was observed for carriers of two functional CYP2D6 alleles combined with only one functional CYP2C19 allele [0 of 13 (0%) vs 9 of 11 (81.8%) for the high-risk group; P = 0.00004]. We found no correlations between drug concentrations or genotypes and therapeutic response. CONCLUSIONS: Combined pharmacogenetic testing for CYP2D6 and CYP2C19 identifies patients with low risk for side effects in amitriptyline therapy and could possibly be used to individualize antidepressive regimens and reduce treatment cost. Identification of genotypes associated with slightly reduced intermediate metabolism may be more important than currently anticipated. It could also be the key to demonstrating cost-effectiveness for CYP2D6 genotyping in critical dose drugs.