originally proposed by Hurwitz and Wade (99). Wilke et al. (100) provided a well-organized description of anticipated drug reactions and unanticipated ADRs. Anticipated ADRs include those that are extensions of the drug's intended therapeutic effect.

In contrast, examples of unanticipated ADRs that seem not to be related to lowering cholesterol include the effect of statins (cholesterol-lowering drug) in causing myalgia (muscle pain). Unanticipated ADRs also encompass those resulting in a response to the drug, by patients having specific genetic mutations.

Wilke et al. (101) identified a number of mutations, in human patients, that can give rise to unanticipated ADRs. These mutations include the CYP2C9 and VKORC1 mutations, which increase risk for bleeding during warfarin treatment (102), mutations in glucose-6-phosphate dehydrogenase can give rise to hemolytic anemia during treatment with sulfonylurea drugs, as is the case with glipizide, a drug that stimulates the pancreas to secrete insulin in diabetics (103), and mutations in UDP-glucuronosyl transferase 1A1 (UGT1A1) can give rise to neutropenia, with administration of the anticancer drug irinotecan (104). The package inserts for these drugs identify these mutations, and warn of the ADRs, as indicated in the footnoted package inserts.

III. QT INTERVAL PROLONGATION

a. Introduction

Cardiac drug safety information is captured on a routine basis in various types of clinical trials, for example, in clinical trials for oncology drugs and antibiotics (105,106,107). Cardiac adverse event information is provided by electrocardiograms (ECG) and, in particular, by a pattern on the ECG called the "QT interval." Instructions for monitoring the QT interval and other parameters of cardiac physiology are sometimes included in the Clinical

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