prolong the QT interval by blocking cardiac potassium ion channels, more specifically, the potassium channel responsible for the rapid repolarizing current I_{Kr} (126). The "mouth" of this channel is unusually wide for a potassium ion-selective channel, permitting access to many drugs. The channel is composed of proteins encoded for by two genes. The human ether-related a-go-go (*HERG*) gene encodes for the pore-forming HERG protein and the *KCNE2* gene encodes for the accessory protein, MinK-related peptide 1 (127). In addition to acting directly at the mouth of the HERG protein, other mechanisms for drug-induced QTc prolongation include blockade of both I_{Kr} and I_{Ks}, as occurs with azimilidine, and inhibition of HERG trafficking to the cell membrane, as occurs with pentamidine and arsenic trioxide (128). The term, trafficking to the cell membrane, refers to the process where newly biosynthesized polypeptides, which are destined to be membrane-bound proteins, are inserted into the plasma membrane. Fluoxetine, which is an antidepressant, prolongs the QTc interval by two mechanisms, direct block of the HERG channel and disruption of HERG trafficking to the cardiac cell membrane (129).

According to various commentators (130,131), the relation between QT prolongation and the risk of TdP is complex and unpredictable. Assessment of risk for TdP versus the health benefit of any drug, may be finely balanced, thus impairing clear-cut individual clinical judgments. The resulting problem for drug safety monitoring is as follows. Torsades de pointes and sudden death are unpredictable and rare. The detection of these adverse events requires large sample sizes that are achieved only after a drug is on the market (132). Regarding this point, another commentator stated that, "[e]ven in the presence of QT prolongation, however TdP may occur as rarely as once in every 10,000 patient-years of exposure to a compound … clinical TdP is notoriously difficult to assess during the pharmaceutical development process" (133).

The mechanism by which QT prolongation leads to torsades de pointes is outlined in an excellent review by Nachimuthu et al. (134).

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