in most people, but does not have this effect in a fraction of the population (47). This warning is:

> [a] fraction of the population (about 7% of Caucasians and 2% of African Americans) ... have reduced activity in [CYP2D6] resulting in ... higher ... plasma concentrations ... of atomoxetine compared with people with normal activity. Drugs that inhibit CYP2D6, such as fluoxetine, paroxetine, and quinidine, cause similar increases in exposure.

The package insert warns that, where fluoxetine is co-administered with atomoxetine, the result is atomoxetine-specific adverse reactions, such as liver injury and jaundice.

g. Transporters

Konig et al. (48) provide an excellent account of drug–drug interaction studies that involve transporters. These include transporters that are dedicated to mediating either entry into cells, or mediating efflux of drugs out of cells. In drug–drug interaction studies, the transporters of greatest interest include the hepatic transporters, OATPB1 and OATP1B3, and the transporters mediating efflux, such as P-glycoprotein (Pgp), Breast Cancer Resistance Protein (BCRP), and Multi-Drug Resistance Protein 2 (MRP2). Despite being named BCRP, this efflux transporter is expressed by intestines, liver, kidney, and brain. OATP means "Organic Anion-Transporting Protein."

h. Drug–Drug interactions Between Statins and Cyclosporin A

Statins, such as atorvastatin (Lipitor®), reach their target enzyme in liver cells by way of the transporter, OATP1B1. This transporter is a membrane-bound protein on hepatocytes (49). Impaired transport of atorvastatin into liver cells occurs with naturally occurring variants of OATP1B1 in the human population. A knowledge of the genotype of the gene encoding this transporter, for any given patient, can predict whether statin therapy in that patient will be reduced because of that impairment. In other words, if the statin cannot enter the hepatocyte, the statin will not work.

Naturally occurring variants in OATP1B1 can impair the transport activity of OATP1B1 and, as a consequence, result in unexpectedly high levels of any statin drugs that are administered. This scenario is illustrated by the following excerpts from Nies et al. (50):

"The common variant c.521T > C (rs4149056; Val174Ala) is highlighted by a genome-wide association study (GWAS) suggesting an increased risk for simvastatin-induced myopathy in variant carriers."

"The increased atorvastatin [plasma concentration] ... in carriers of the *15 haplotype in our pharmacokinetic study revealed impaired atorvastatin uptake, indicating that the variant OATP1B1*15 protein is associated with decreased intrinsic transport activity."

The quotations refer to the variants in OATP1B1 that are the Val174Ala variant and

[47]STRATTERA® (atomoxetine) CAPSULES for Oral Use; April 2015 (18 pp.).

[48]Konig J, et al. Transporters and drug-drug Interactions: important determinants of drug disposition and effects. Pharmacol. Rev. 2013;65:944–96.

[49]Kunze A, et al. Prediction of OATP1B1 and OATP1B3 mediated hepatic uptake of statins based on transporter protein expression and activity data. Drug Metab. Dispos. 2015;43:424–32.

[50]Nies AT, Niemi M, Burk O, et al. Genetics is a major determinant of expression of the human hepatic uptake transporter OATP1B1, but not of OATP1B3 and OATP2B1. Genome Med. 2013;5:1 (11 pp.).