Overview of Azole Metabolism and Drug Interactions

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<th>Inhibitor</th>
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<td>P-gp</td>
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*CYP 2C19 polymorphisms: 15-20% Asians, 3-5% of Caucasians, Blacks are poor metabolizers

**Note:** see below for factors impacting extent of, onset/offset of interactions

### Select substrates of shared CYP pathways

- **3A4 substrates:**
  - amiodarone, dronedarone, many statins (e.g. atorvastatin, lovastatin, simvastatin), methadone, suvorexant, guanfacine
  - tacrolimus, cyclosporine, sirolimus, everolimus, prednisolone (the active metabolite of prednisone)
  - rivaroxaban, apixaban, edoxaban (minor), warfarin (minor)
  - rifampin (weak- other pathways), rifabutin, letermovir (minor) maribavir, venetoclax, midostaurin, ivosidenib, TKIs (gilteritinib, ibrutinib, ponatinib, dasatinib)
- **3A4 inducer:** rifampin, rifabutin, phenobarbital, phenytoin, carbamazepine
- **3A4 inhibitor:** ritonavir (strong), maribavir (weak), cyclosporine (weak)
- **2C9 substrate:** warfarin, phenytoin
- **2C19 substrate:** warfarin, clopidogrel
- **UGT substrate:** mycophenolate
- **UGT inducer:** rifampin, rifabutin
- **P-gp substrate:** digoxin, tacrolimus, cyclosporine, sirolimus, everolimus, rifampin, rivaroxaban, apixaban, edoxaban, dabigatran, letermovir
- **P-gp inhibitor:** amiodarone, ritonavir, maribavir

### Timeline for enzyme induction & inhibition

- **Onset**
  - Inhibition occurs quickly (days).
    - e.g. Max CYP3A4 inhibition observed within 2 days with voriconazole use
    - Note: dose-dependent (e.g. fluconazole 100mg vs 800mg)
  - CYP induction can take up to 14 days since this is via increased synthesis or decreased breakdown of CYP isoenzymes.
- **Offset**
  - Can vary depending on various factors, e.g. age (elderly → slower offset), mechanism of CYP inhibition (reversible vs irreversible), half-life of drug, duration of drug use prior to and during interaction.
References:


