

Supplementary Materials: Prediction of CYP-mediated drug interaction using physiologically based pharmacokinetic modeling: A case study of salbutamol and fluvoxamine

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Table S1. List of potential salbutamol-interacting drugs, belonging to different drug classes, from corticosteroids to antidepressants.

| Drug | Drug Class |
|------------------------|--|
| Atenolol | β -blocker |
| Beclomethasone | Corticosteroid |
| Doxepin | Tricyclic antidepressant |
| Fluticasone Propionate | Corticosteroid |
| Fluticasone | Corticosteroid |
| Formoterol | Long-acting β -agonist |
| Furosemide | Diuretic |
| Isocarboxazid | Monoamine oxidase inhibitor |
| Ketotifen | Antihistamine |
| Methylprednisolone | Corticosteroid |
| Prednisolone | Corticosteroid |
| Prednisone | Corticosteroid |
| Propranolol | β -blocker |
| Rosiglitazone | Thiazolidinedione |
| Salmeterol | Long-acting β -agonist |
| Theophylline | Xanthine |
| Fluvoxamine | Selective serotonin reuptake inhibitor |

Table S2. PBPK models and respective individuals' characteristics.

| PBPK Model | Population | Gender | Age (years) | Health Status | Height (cm) | Weight (kg) | BMI (kg/m ²) | Body Fat (%) |
|------------|------------|--------|-------------|---------------------------|-------------|-------------|--------------------------|--------------|
| 1 | American | Male | 30 | Healthy | 176.43 | 75.0 | 24.0944 | 23.41 |
| 2 | American | Male | 10 | Healthy | 145.23 | 38.9 | 18.4432 | 17.18 |
| 3 | American | Male | 65 | Healthy | 173.76 | 75.0 | 24.8406 | 24.08 |
| 4 | American | Male | 30 | Mild Renal Impairment | 176.43 | 75.0 | 24.0944 | 23.41 |
| 5 | American | Male | 30 | Moderate Renal Impairment | 176.43 | 75.0 | 24.0944 | 23.41 |
| 6 | American | Male | 30 | Severe Renal Impairment | 176.43 | 75.0 | 24.0944 | 23.41 |
| 7 | American | Male | 30 | Healthy (Overweight) | 176.43 | 85.53 | 27.4773 | 26.34 |
| 8 | American | Male | 30 | Healthy (Obese) | 176.43 | 105.0 | 33.7322 | 31.80 |
| 9 | American | Female | 30 | Healthy | 162.20 | 65.0 | 24.71 | 33.28 |
| 10 | American | Female | 30 | Healthy (Pregnant) | 162.20 | 65.0 | 24.71 | 33.28 |

BMI, Body Mass Index

Table S3. Metabolic profile of the 17 potential salbutamol-interacting drugs, estimated by ADMET Predictor[®].

| Drug | CYP Enzyme | Inhibitor | Substrate | K _m | V _{max} | CL | Sites of metabolism |
|----------------|------------|-----------|-----------|----------------|------------------|--------|---------------------|
| Atenolol | 1A2 | No (63%) | No (90%) | NS | NS | NS | NS |
| | 2A6 | ND | No (98%) | NS | NS | NS | NS |
| | 2B6 | ND | No (98%) | NS | NS | NS | NS |
| | 2C8 | ND | No (92%) | NS | NS | NS | NS |
| | 2C9 | No (95%) | Yes (98%) | NS | NS | NS | NS |
| | 2C19 | No (99%) | Yes (39%) | 74.179 | 422.087 | 79.662 | C17, C7 |
| | 2D6 | Yes (46%) | Yes (66%) | 0.778 | 1.291 | 13.282 | C17, C7 |
| | 2E1 | ND | No (98%) | NS | NS | NS | NS |
| | 3A4 | No (78%) | No (84%) | NS | NS | NS | NS |
| Beclomethasone | 1A2 | No (82%) | No (97%) | NS | NS | NS | NS |
| | 2A6 | ND | No (98%) | NS | NS | NS | NS |
| | 2B6 | ND | Yes (71%) | ND | ND | ND | C28, C34 e C27 |
| | 2C8 | ND | No (63%) | NS | NS | NS | NS |
| | 2C9 | No (99%) | No (98%) | NS | NS | NS | NS |
| | 2C19 | No (95%) | No (88%) | 74.179 | 422.087 | 79.662 | C17, C7 |
| | 2D6 | No (95%) | No (95%) | 0.778 | 1.291 | 13.282 | C17, C7 |
| | 2E1 | ND | No (84%) | NS | NS | NS | NS |
| | 3A4 | Yes (80%) | Yes (89%) | 40.448 | 16.885 | 46.338 | C7, C33 e C27 |

| | | | | | | | |
|------------------------|------|-----------|-----------|----------|----------|--------|------------------------------|
| Doxepin | 1A2 | No (97%) | Yes (91%) | 23.920 | 10.658 | 23.171 | C20 e C21 |
| | 2A6 | ND | No (70%) | NS | NS | NS | NS |
| | 2B6 | ND | Yes (89%) | ND | ND | ND | C20, C21 e C11 |
| | 2C8 | ND | Yes (91%) | ND | ND | ND | C20, C21 |
| | 2C9 | No (90%) | Yes (66%) | 5.823 | 0.149 | 1.867 | C20, C21 |
| | 2C19 | Yes (31%) | Yes (82%) | 69.614 | 15.082 | 3.033 | C20, C21 |
| | 2D6 | Yes (51%) | Yes (87%) | 3.417 | 7.545 | 17.667 | C20, C21, C13 e C11 |
| | 2E1 | ND | No (69%) | NS | NS | NS | NS |
| | 3A4 | No (90%) | Yes (74%) | 74.034 | 4.391 | 6.584 | C20, C21 |
| Fluticasone Propionate | 1A2 | No (76%) | No (97%) | NS | NS | NS | NS |
| | 2A6 | ND | No (98%) | NS | NS | NS | NS |
| | 2B6 | ND | Yes (44%) | ND | ND | ND | S28 |
| | 2C8 | ND | No (86%) | NS | NS | NS | NS |
| | 2C9 | No (99%) | No (88%) | NS | NS | NS | NS |
| | 2C19 | No (89%) | No (88%) | NS | NS | NS | NS |
| | 2D6 | No (95%) | No (85%) | NS | NS | NS | NS |
| | 2E1 | ND | No (76%) | NS | NS | NS | NS |
| | 3A4 | Yes (80%) | Yes (98%) | 19.997 | 6.993 | 39.033 | S28, C7, C33 e C29 |
| Fluticasone | 1A2 | No (90%) | No (97%) | NS | NS | NS | NS |
| | 2A6 | ND | No (98%) | NS | NS | NS | NS |
| | 2B6 | ND | Yes (61%) | ND | ND | ND | S28 |
| | 2C8 | ND | Yes (58%) | ND | ND | ND | C29, S28, C16, C24, C19 e C7 |
| | 2C9 | No (99%) | No (96%) | NS | NS | NS | NS |
| | 2C19 | No (94%) | No (88%) | NS | NS | NS | NS |
| | 2D6 | No (95%) | No (95%) | NS | NS | NS | NS |
| | 2E1 | ND | No (71%) | NS | NS | NS | NS |
| | 3A4 | Yes (38%) | Yes (98%) | 40.068 | 1.515 | 4.197 | S28, C7, C29 |
| Formoterol | 1A2 | Yes (58%) | No (97%) | NS | NS | NS | NS |
| | 2A6 | ND | No (94%) | NS | NS | NS | NS |
| | 2B6 | ND | No (98%) | NS | NS | NS | NS |
| | 2C8 | ND | No (92%) | NS | NS | NS | NS |
| | 2C9 | No (95%) | No (98%) | NS | NS | NS | NS |
| | 2C19 | No (96%) | No (88%) | NS | NS | NS | NS |
| | 2D6 | Yes (70%) | Yes (87%) | 5.614 | 8.237 | 11.739 | C19, C23 |
| | 2E1 | ND | No (98%) | NS | NS | NS | NS |
| | 3A4 | No (46%) | No (48%) | NS | NS | NS | NS |
| Furosemide | 1A2 | No (86%) | No (97%) | NS | NS | NS | NS |
| | 2A6 | ND | No (70%) | NS | NS | NS | NS |
| | 2B6 | ND | No (98%) | NS | NS | NS | NS |
| | 2C8 | ND | No (77%) | NS | NS | NS | NS |
| | 2C9 | Yes (49%) | Yes (45%) | 5.540 | 3.661 | 48.237 | C2 e C6 |
| | 2C19 | Yes (99%) | Yes (82%) | 1813.378 | 3637.938 | 38.086 | C6, C2 e C1 |
| | 2D6 | No (55%) | No (68%) | NS | NS | NS | NS |
| | 2E1 | ND | Yes (82%) | ND | ND | ND | C2 |
| | 3A4 | No (80%) | No (38%) | NS | NS | NS | NS |
| Isocarboxazid | 1A2 | Yes (95%) | Yes (74%) | 524.501 | 15.319 | 1.519 | C7, C17 e C3 |
| | 2A6 | ND | Yes (82%) | ND | ND | ND | C7, C17, N13 e C3 |
| | 2B6 | ND | No (89%) | NS | NS | NS | NS |
| | 2C8 | ND | Yes (58%) | ND | ND | ND | C7, C17 e C3 |
| | 2C9 | Yes (41%) | No (88%) | NS | NS | NS | NS |
| | 2C19 | No (78%) | Yes (61%) | 57.052 | 132.576 | 32.533 | C17 e C7 |
| | 2D6 | No (95%) | No (68%) | NS | NS | NS | NS |
| | 2E1 | ND | Yes (40%) | ND | ND | ND | C7, C3 e N13 |
| | 3A4 | Yes (51%) | No (58%) | NS | NS | NS | NS |

| | | | | | | | |
|--------------------|------|-----------|-----------|---------|--------|--------|------------------------|
| Ketotifen | 1A2 | No (90%) | Yes (91%) | 139.473 | 9.355 | 3.488 | C22 e N19 |
| | 2A6 | ND | Yes (ND) | ND | ND | ND | C22 e C12 |
| | 2B6 | ND | No (ND) | NS | NS | NS | NS |
| | 2C8 | ND | No (77%) | NS | NS | NS | NS |
| | 2C9 | No (ND) | Yes (ND) | 21.787 | 0.107 | 0.359 | C22 |
| | 2C19 | Yes (ND) | Yes (ND) | 50.763 | 5.845 | 1.612 | C22 |
| | 2D6 | Yes (55%) | Yes (ND) | 21.857 | 27.720 | 10.146 | C22, C12, C7, C3 e N19 |
| | 2E1 | ND | No (76%) | NS | NS | NS | NS |
| | 3A4 | No (90%) | Yes (92%) | 53.902 | 4.131 | 8.507 | C22, N19 e C12 |
| Methylprednisolone | 1A2 | No (97%) | No (97%) | NS | NS | NS | NS |
| | 2A6 | ND | No (98) | NS | NS | NS | NS |
| | 2B6 | ND | Yes (47%) | ND | ND | ND | C25 |
| | 2C8 | ND | No (66%) | NS | NS | NS | NS |
| | 2C9 | No (99%) | No (98%) | NS | NS | NS | NS |
| | 2C19 | No (95%) | No (99%) | NS | NS | NS | NS |
| | 2D6 | No (95%) | No (95%) | NS | NS | NS | NS |
| | 2E1 | ND | No (78%) | NS | NS | NS | NS |
| | 3A4 | Yes (46%) | Yes (98%) | 92.176 | 37.806 | 45.527 | C7, C25 e C13 |
| Prednisolone | 1A2 | No (97%) | No (97%) | NS | NS | NS | NS |
| | 2A6 | ND | No (98%) | NS | NS | NS | NS |
| | 2B6 | ND | Yes (46%) | ND | ND | ND | C24 e C12 |
| | 2C8 | ND | No (77%) | NS | NS | NS | NS |
| | 2C9 | No (99%) | No (98%) | NS | NS | NS | NS |
| | 2C19 | No (97%) | No (95%) | NS | NS | NS | NS |
| | 2D6 | No (95%) | No (95%) | NS | NS | NS | NS |
| | 2E1 | ND | No (80%) | NS | NS | NS | NS |
| | 3A4 | Yes (38%) | Yes (92%) | 83.372 | 24.021 | 31.981 | C7, C24 e C12 |
| Prednisone | 1A2 | No (97%) | No (90%) | NS | NS | NS | NS |
| | 2A6 | ND | No (98%) | NS | NS | NS | NS |
| | 2B6 | ND | Yes (49%) | ND | ND | ND | C23 |
| | 2C8 | ND | No (80%) | NS | NS | NS | NS |
| | 2C9 | No (99%) | No (98%) | NS | NS | NS | NS |
| | 2C19 | No (98%) | No (95%) | NS | NS | NS | NS |
| | 2D6 | No (95%) | No (95%) | NS | NS | NS | NS |
| | 2E1 | ND | No (84%) | NS | NS | NS | NS |
| | 3A4 | Yes (46%) | Yes (98%) | 74.801 | 11.076 | 16.436 | C7, C23 |
| Propanolol | 1A2 | No (61%) | No (97%) | NS | NS | NS | NS |
| | 2A6 | ND | No (98%) | NS | NS | NS | NS |
| | 2B6 | ND | No (73%) | NS | NS | NS | NS |
| | 2C8 | ND | No (92%) | NS | NS | NS | NS |
| | 2C9 | No (92%) | No (98%) | NS | NS | NS | NS |
| | 2C19 | No (65%) | No (99%) | NS | NS | NS | NS |
| | 2D6 | No (55%) | Yes (87%) | 3.901 | 1.458 | 2.990 | C17 |
| | 2E1 | ND | No (98%) | NS | NS | NS | NS |
| | 3A4 | No (90%) | No (58%) | NS | NS | NS | NS |
| Rosiglitazone | 1A2 | No (90%) | No (91%) | NS | NS | NS | NS |
| | 2A6 | ND | No (63%) | NS | NS | NS | NS |
| | 2B6 | ND | No (78%) | NS | NS | NS | NS |
| | 2C8 | ND | Yes (83%) | ND | ND | ND | C23 e C4 |
| | 2C9 | Yes (63%) | Yes (66%) | 117.900 | 8.272 | 5.122 | S19, C23, C4 e C5 |
| | 2C19 | Yes (23%) | Yes (82%) | 15.478 | 0.964 | 0.872 | C23, S19 e C9 |
| | 2D6 | No (95%) | Yes (56%) | 9.274 | 11.191 | 9.654 | S19, C4 e C23 |
| | 2E1 | ND | Yes (70%) | ND | ND | ND | S19, C4 e C23 |
| | 3A4 | No (67%) | Yes (82%) | 35.382 | 4.836 | 15.171 | C23 e S19 |
| Salmeterol | 1A2 | Yes (72%) | No (97%) | NS | NS | NS | NS |

| | | | | | | | |
|--------------|------|-----------|-----------|---------|--------|--------|-------------------------|
| | 2A6 | ND | No (94%) | NS | NS | NS | NS |
| | 2B6 | ND | No (83%) | NS | NS | NS | NS |
| | 2C8 | ND | No (99%) | NS | NS | NS | NS |
| | 2C9 | No (90%) | No (90%) | NS | NS | NS | NS |
| | 2C19 | No (91%) | No (72%) | NS | NS | NS | NS |
| | 2D6 | Yes (70%) | Yes (72%) | 3.054 | 37.871 | 99.216 | C7, C20, C11, C23 e C27 |
| | 2E1 | ND | No (82%) | NS | NS | NS | NS |
| | 3A4 | Yes (51%) | No (51%) | NS | NS | NS | NS |
| Theophylline | 1A2 | No (86%) | Yes (91%) | 173.268 | 1.901 | 0.570 | C12 e C7 |
| | 2A6 | ND | Yes (82%) | ND | ND | ND | C12 |
| | 2B6 | ND | No (75%) | NS | NS | NS | NS |
| | 2C8 | ND | No (99%) | NS | NS | NS | NS |
| | 2C9 | No (99%) | No (72%) | NS | NS | NS | NS |
| | 2C19 | No (98%) | No (95%) | NS | NS | NS | NS |
| | 2D6 | No (95%) | No (95%) | 3.054 | 37.871 | 99.216 | C7, C20, C11, C23 e C27 |
| | 2E1 | ND | Yes (49%) | ND | ND | ND | C7, C10 e C12 |
| | 3A4 | No (81%) | No (38%) | NS | NS | NS | NS |

ND, not defined; NS, no substrate