

# Quick Reference GUIDE to Cytochrome p450 Action of Medicinal Agents Used in PWS

DISCLAIMER: This guide is a QUICK REFERENCE. It has been approved for use by the members of the Clinical Advisory Board of PWSA (4/14/2018). It is not a complete list of medicinal agents used in persons with PWS, and cytochrome (CYP) information provided may not be all inclusive. When using this guide, please check Flockhart to verify. THIS IS A WORKING DOCUMENT. Please contact me if you find any new information, or if there are other medicinals to be added to the list. *This document provides a canvas and some paint, but the clinician is the artist!* Remember, medicinal agents may be active at multiple cytochrome sites with varying affinities. Pharmacokinetics will vary according to the dose of the agent, the mode of delivery, the form of the agent (immediate acting, sustained or extended release), the CYP status (ultra-rapid, extensive, intermediate, or poor) and the presence of other drugs using that/those CYP pathways.

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# Cytochrome p450 Pharmacokinetic Action

- Substrate
  - The enzyme to which the drug selectively binds
    - Some drugs use more than one enzyme
    - Competition with other drugs that use the enzyme as a substrate (common cause of drug-drug interaction)
- Inducer
  - A drug that causes an increase in the production of the enzyme
    - Acts at the promoter site on the gene
    - Takes 1-2 weeks for effect to occur
    - CYP2D6 is the only cytochrome that cannot be induced
- Inhibitor
  - Binds to the enzyme and blocks its use
    - Immediate effect

# Reference

<http://medicine.iupui.edu/flockhart/>

| CYP1A2 | CYP2B6                 | CYP2C19                       | CYP2C9                     | CYP2D6                     | CYP3A4-5 |
|--------|------------------------|-------------------------------|----------------------------|----------------------------|----------|
|        | ↓ in 10%<br>Caucasians | Absent in<br>15-30%<br>Asians | Absent in 1%<br>Caucasians | Absent in 7%<br>Caucasians |          |

# Psychotropic Medications Used Frequently in Persons with PWS

The following list of medications has been generated from clinical experience. It is *not* a complete list of medications used, nor is it a list of *recommended* medications. Pertinent information about cytochrome (CYP) metabolism was obtained through the reference book below and updated by literature review. Agents metabolized by more than one cytochrome (CYP) as substrates are numbered 1,2,3 to indicate primary and secondary pathways.

Bibliography: Mrazek, David A. Psychiatric Pharmacogenomics. Oxford Press. 2010.

| Cytochrome | CYP1A2   | CYP2B6   | CYP2C19  | CYP2C9  | CYP2D6  | CYP3A4-5  |
|------------|--|--|--|---|---|---|
| Substrate  | Acetaminophen<br>Amitriptyline,3<br>Chlorpromazine,2<br>Clomipramine,2<br>Clozapine,1<br>Duloxetine,1<br>Imipramine,2<br>Fluvoxamine,1<br>Haloperidol,3<br>Mirtazapine,3<br>Olanzapine,1<br>Propranolol<br>Tacrine<br>Thioridazine,2 | Bupropion,1<br>Selegiline<br>Sertraline,1<br>Sibutramine | Amitriptyline,1<br>Citalopram,1<br>Clomipramine,1<br>Clozapine,2<br>Diazepam<br>Doxepin,2<br>Escitalopram,1<br>Fluoxetine<br>Imipramine,1<br>Nortriptyline,2<br>Phenytoin<br>Sertraline,2<br>Venlafaxine,2 | Amitriptyline,2<br>Celecoxib<br>Fluoxetine,2<br>Sertraline,3<br>Valproate<br>Warfarin | Amitriptyline,2<br>Aripiprazole,2<br>Asenapine<br>Bupropion,2<br>Chlorpromazine,1<br>Citalopram,3<br>Clomipramine,4<br>Clozapine,3<br>Desipramine,1<br>Doxepin,1<br>Duloxetine,2<br>Escitalopram,3<br>Fluoxetine,1<br>Fluvoxamine,2<br>Haloperidol,1<br>Imipramine,2<br>Mirtazapine,2<br>Nortriptyline,1<br>Olanzapine,2<br>Paroxetine,1<br>Perphenazine<br>Quetiapine,2<br>Risperidone,1<br>Sertraline,2<br>Thioridazine,1<br>Trazadone,2<br>Venlafaxine,1<br>Ziprasidone, 3 | Alprazolam<br>Aripiprazole,1<br>Bupropion,2<br>Buspirone<br>Citalopram,2<br>Clomipramine,3<br>Clonazepam<br>Carbamazepine<br>Desvenlafaxine<br>Dextromethorphan<br>Duloxetine,3<br>Escitalopram,2<br>Erythromycin<br>Haloperidol,2<br>Lurasidone<br>Mirtazapine,1<br>Quetiapine,1<br>Risperidone,2<br>Sertraline,3<br>Trazadone,1<br>Tiagabine<br>Ziprasidone,1 |

# The following agents are inhibitors or inducers of specific cytochrome enzymes:

| Cytochrome | CYP1A2  | CYP2B6  | CYP2C19   | CYP2C9   | CYP2D6  | CYP3A4-5  |
|------------|---|---|---|--|---|---|
| Inhibitor  | Celecoxib<br>Cimetidine<br>Citalopram<br>Ciprofloxacin<br>Clarithromycin<br>Erythromycin<br>Estradiol<br>Fluvoxamine<br>Isoniazid<br>Ketoconazole |   | Cimetidine<br>Citalopram<br>Fluconazole<br>Fluoxetine<br>Fluvoxamine<br>Indomethacin<br>Isoniazid<br>Ketoconazole<br>Lansoprazole<br>Modafanil<br>Omeprazole<br>Oxcarbazepine<br>Probenecid<br>Topiramate | Cimetidine<br>Contraceptives<br>Fluconazole<br>Fluoxetine<br>Fluvoxamine<br>Isoniazid<br>Ketoconazole<br>Methylphenidate<br>Modafanil<br>Omeprazole<br>Paroxetine<br>Sertraline<br>Sulfonamides<br>Tacrine | Asenapine<br>Bupropion<br>Benadryl<br>Fluoxetine<br>Haloperidol<br>Hydroxyzine<br>Methylphenidate<br>Paroxetine<br>Propranolol<br>Quinidine<br>Ranitidine | Cimetidine<br>Ciprofloxacin<br>Clarithromycin<br>Cyclosporine<br>Erythromycin<br>Grapefruit<br>Isoniazid<br>Ketoconazole<br>Prednisone<br>Sertraline<br>Verapamil |
| Inducer    | Carbamazepine<br>Cruciferous veg<br>Tobacco<br>Cannabis<br>Char-grilling  | Carbamazepine<br>Phenytoin<br>Phenobarbital<br>Rifampin | Rifampin  | Carbamazepine<br>Phenobarbital<br>Rifampin<br>St John's wort   |   | Carbamazepine<br>Crucif veg<br>Phenytoin<br>Rifampin<br>St John's wort  |

The following medicinal or OTC agents are grouped by type of drug:

| Medicinal or OTC drugs          | Action/Cytochrome p450      |
|---------------------------------|-----------------------------|
| Analgesics:                     |                             |
| • NSAIDs                        | Substrate 2C9               |
| – Celecoxib                     | Substrate 2C9, Inhibits 1A2 |
| • Acetaminophen                 | Substrate 1A2               |
| • Codeine                       | Substrate 2D6               |
| • Oxycodone                     | Substrate 2D6               |
| • Tramadol                      | Substrate 2D6               |
| Anesthetics: Ketamine, Propofol | Substrate 2B6               |
| Anti-migraine: Zolmitriptan     | Substrate 1A2               |
| Antibiotics/antifungal:         |                             |
| • Erythromycin                  | Substrate 3A4               |
| • Ciprofloxacin                 | Inhibits 1A2                |
| • Clarithromycin                | Inhibits 1A2                |
| • Ketoconazole                  | Inhibits 3A4, 2C19          |

| Medicinal or OTC drugs       | Action/Cytochrome p450        |
|------------------------------|-------------------------------|
| Antihistamine/decongestant:  |                               |
| • Benadryl (diphenhydramine) | Inhibits 2D6                  |
| • Claritin (loratadine)      | Substrate 2D6                 |
| • Fexofenadine               | Substrate 3A4                 |
| • Dextromethorphan           | Substrate 2D6, 3A4            |
| Diet:                        |                               |
| • Grapefruit juice           | Inhibits 3A4                  |
| • Char-grilled meats         | Inhibits 1A2                  |
| • Cruciferous vegetables     | Induces 1A2, 3A4              |
| GI:                          |                               |
| • Zantac (ranitidine)        | Substrate 2D6                 |
| • Tagamet (cimetidine)       | Inhibits 3A4, 1A2, 2C19       |
| • Prilosec (omeprazole)      | Substrate 2C19; inhibits 2C19 |
| • Propulsid (cisapride)      | Substrate 3A4                 |
| Metformin                    | Downregulates aromatase 19A1  |



| Medicinal or OTC drugs     | Action/Cytochrome p450                             |
|----------------------------|--|
| Oral hypoglycemics         | Substrate 2C9                                      |
| Respiratory: Theophylline  | Substrate 1A2                                      |
| Sleep:                     |  |
| • Modafanil/Nuvigil        | Induces 1A2, 3A4; inhibits 2C19                    |
| • Melatonin                | Substrate 1A2                                      |
| • Zolpidem                 | Substrate 3A4                                      |
| Steroids:                  |  |
| • Human Growth Hormone     | Induces 1A2; inhibits 2C19                         |
| • Estradiol/testosterone   | Substrate 1A2/3A4                                  |
| • Cortisol                 | Substrate 3A4                                      |
| Stimulants/non-stimulants: |  |
| • Amphetamine              | Substrate 2D6                                      |
| • Methylphenidate          | Substrate & weak inhibitor 2D6; Inhibits 3A4, 2C19 |
| • Atomoxetine              | Substrate 2D6                                      |

| Medicinal or OTC drugs   | Action/Cytochrome p450   |
|--|--------------------------|
| Substances:  |                          |
| <ul style="list-style-type: none"> <li data-bbox="175 239 430 287">• Caffeine</li> </ul> | Substrate 1A2            |
| <ul style="list-style-type: none"> <li data-bbox="175 325 430 372">• Tobacco</li> </ul>  | Induces 1A2              |
| <ul style="list-style-type: none"> <li data-bbox="175 411 452 458">• Cannabis</li> </ul> | Substrate 2C9, 2C19, 3A4 |