

## Meandering Toward P-Glycoproteins

I think it was Barbara Mandrell who sang “I Was Country When Country Wasn’t Cool”. I piggyback off of that sentiment and say “I Was Psychopharmacologic Before Psychopharmacology Was Cool.” It is hard to imagine now but, when I was reviewing psych nursing textbooks in the mid-1980’s in order to justify adding my book to the field, drugs were rarely mentioned. The hostility toward the medical model was so pronounced that drugs and even accepted diagnoses (e.g. schizophrenia) were avoided if possible. As I have recalled in other places over the years, my allegiance to medications was probably linked to my many years at a state hospital. That said, appreciating psychotropic drugs and understanding them are two different things.

For me, gaining an understanding was a bumpy process- 2 steps forward and 1 step back as they say. As I sit here, I ponder- ‘what are the things that helped me?’. Perhaps, foremost, in about 1984, Dr. Marshal Shlafer asked me to write 5 chapters on psychopharmacology for his new pharmacology textbook (where he got my name I never knew). Beyond the clarifying power of writing, two books stand out in my memory though there were many others, 1) Concepts in Biochemistry: A Programmed Text by William Stephenson (1967) and 2) Drug Interaction Principles for Medical Practice by Kelly Cozza, et al (2003 and before). With Stephenson I kept having “aha” moments. Since I already knew a fair bit, he helped me anchor information that was floating around in my size 7.5 orb. Cozza, on the other hand, taught me stuff I didn’t know and there was quite a bit of that.

One of the most fascinating pieces I picked up from Cozza was the understanding of P-glycoproteins. Prior to Cozza, my understanding of P-450 cytochrome enzymes coupled with my understanding of the blood brain barrier/lipid solubility pretty much composed my world of bioavailability and brain penetration of psychoactive agents. The idea that another mechanism was also at work was foreign to me.

P-glycoproteins are also known as drug-resistance proteins. This mechanism is basically an efflux pump that turns some drugs around in the gut back into the intestinal lumen. P-glycoproteins also serve as part of the blood brain barrier. That is, some drugs, even though they are lipid soluble, cannot pass into the brain because these transporters “kick them out”. Cozza, et al’s example of second-generation antihistamines was the “aha” moment in this text. Second-generation antihistamines such as loratadine do not cause drowsiness like diphenhydramine because loratadine is transported back out of the brain by P-glycoproteins. The P-glycoprotein system can be inhibited (e.g. fluphenazine, grapefruit juice, haloperidol)- thus more of a drug enters the brain, or it can be induced (e.g. St. John’s wort, trazodone, prazosin)- less drug enters the brain. Of course, not all drugs are substrates of the P-glycoprotein system but Cozza lists about 45, some of which are psychotropics. But learning the list of psychotropics is not enough. Many of the rest of this group can interact with psychotropic medications, so changes in their bioavailability can cause concern as well.