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### The Pharmacogenomics of Zolpidem: Current Research and Future Avenues

Pharmacogenomics is being used in the study of medications. Increasingly, scientists are looking at the individual genes and bases of DNA to detect changes that may cause differences in drug pharmacodynamics and pharmacokinetics – how a drug works and how fast it metabolizes. One drug that has shown pharmacogenomic properties is zolpidem, the active ingredient in Ambien CR – a sleep aid for insomnia. Insomnia is the inability to sleep, and the vast majority of cases occur as a symptom of some other health condition like asthma or heartburn.<sup>1</sup> Doctors encourage life style changes first, and then prescribe drugs like zolpidem for the condition.<sup>2</sup> Data has shown that patients have widely different responses to zolpidem – indicating a genetic response on its rate of metabolism. Initial evidence has linked the rate to certain genes, and future research in this area will better explain the dosage required for this drug.

The most popular insomnia medication is zolpidem. Sleep aids work by relaxing the body and inducing low levels of sedation. The most well known class is Benzodiazepine (like Valium). However, this class has been associated with abuse.<sup>3</sup> To avoid dependence, drug companies developed non-benzodiazepine hypnotics, a classification that includes zolpidem. The difference between these two classes is explained through pharmacodynamics.

Much of zolpidem's pharmacodynamics in the body is related to the Gamma-Aminobutyric acid receptors in the central nervous system. Both Benzodiazepine and non-Benzodiazepine drugs focus on this GABA receptor. These receptors link with neurotransmitters which work to inhibit muscle

movement throughout the body. In other words, activating this receptor will increase the lethargy of the patient.<sup>4</sup> Benzodiazepine drugs work by assisting the GABA<sub>A</sub> receptor complex that links the GABA neurotransmitter with its receptor. Adding complexity, there are two types of receptors, one that creates a lethargy effect and one that causes an anti-convulsive effect. Benzodiazepine drugs are used in a variety of medical illnesses, including insomnia and seizures.<sup>5</sup> This versatility is a result of Benzodiazepine's affinity for all GABA receptors. While this allows the drug to be widely prescribed, it also means that patients who have just insomnia may have adverse side effects.

Non-Benzodiazepine drugs like zolpidem avoid this problem by preferentially binding to the lethargy receptors. It does do by having a higher affinity to the BZ<sub>1</sub> receptor.<sup>6</sup> The pharmacodynamics of zolpidem is also affected by other substances in the body. GABA receptors are widely targeted by other substances such as alcohol and coffee. One experiment involved the combination of coffee and zolpidem and showed that coffee improved a person's wakefulness, but did not completely undo the sedative effects of the drug.<sup>7</sup> This indicates that coffee has a pharmacodynamic effect on zolpidem. One of the problems with Zolpidem is that patients may feel tired the next day, indicating that they may have had slower metabolism of the drug. This is pharmacokinetics and it is affected by genetics, as seen next.

Zolpidem, like many drugs, has variable release timings depending on the genetics of the user. In general, zolpidem is taken up readily from the gastrointestinal track where it is slowly released through a controlled release formula. The length of time that a tablet of zolpidem lasts in the body is dependent on the speed of metabolism. That speed is set by the Cytochrome P450 subunits, which affect the metabolism of many drugs.<sup>8</sup> For zolpidem, there are several important genes in its metabolism, including CYP3A4, CYP2C9, CYP1A2, CYP2D6.<sup>9</sup>

Due to metabolism effects, the changes in the four genes affecting zolpidem can mean that individuals may experience more or less wakefulness on the day after use. The amount of drug in the system at any one time is a function of its release and the speed of metabolism. In one study published in 2007, several chromosomal differences were noticed in volunteers taking zolpidem. These volunteers had high variability in peak time (from .25 to 3 hours) and peak concentration (from 75 to almost 300 ng/ml). This is particularly alarming given that zolpidem is prescribed in only one dosage size.<sup>10</sup> Comparative genomics is also adding insight. Scientists have investigated mice to detect differences in BZ subunits. Mice that are missing the alpha-1 subunit due to chromosomal changes had a 66% reduced effectiveness in metabolizing zolpidem.<sup>11</sup> These findings provide direct genetic evidence that variations can play a large part of zolpidem's pharmacokinetics.

Considering the number of patients that have adverse reactions (3.5%)<sup>12</sup>, more research needed in the pharmacogenomics of zolpidem. One study found that roughly two-thirds of zolpidem is metabolized in the CYP3A4 gene.<sup>13</sup> PharmGKB tracks SNPs and other genetic polymorphisms to find correlations between variants and phenotypic responses to medications. In this case, it lists several (mostly loss-of-function) variants in CYP3A4 that may affect zolpidem, including the SNPs rs4986909, rs4987161 and rs2740574. Another view is to look at Benzodiazepine drugs, since they bind to the same receptors. Indeed, diazepam (Valium) is affected by polymorphisms in CYP2C19. A study conducted on an Asian sample found that three groups, roughly equal in size, all metabolized diazepam at significantly different rates.<sup>14</sup> These rates controlled the level of CYP3A4 mRNA production – indicating that these polymorphisms may have a connection with zolpidem. As scientists increasingly perform studies on these and other mutations, the exact changes these SNPs make on zolpidem metabolism will be better understood.

Pharmacogenomics is increasingly playing a role in the study of drugs and their effects on the human body. The research on zolpidem is only just beginning, which is unfortunate. Studies and data, as well as the genetic changes seen in certain P450 subunits, indicates that zolpidem metabolism varies widely among different people, in some case, a 400% difference between patients. This can cause unintentional yet severe consequences for those at the wrong dosage. Considering the popularity of this drug and the dangers of fatigue, more research is needed to fully flesh out the pharmacogenomics of zolpidem.

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<sup>1</sup> What is Insomnia? National Heart Lung and Blood Institute. [http://www.nhlbi.nih.gov/health/dci/Diseases/inso/inso\\_what.html](http://www.nhlbi.nih.gov/health/dci/Diseases/inso/inso_what.html)

<sup>2</sup> Insomnia. Mayo Clinic. <http://www.mayoclinic.com/health/insomnia/DS00187>.

<sup>3</sup> Mantooth, Robin. Toxicity, Benzodiazepine. eMedicine. <http://emedicine.medscape.com/article/813255-overview>

<sup>4</sup> Ambien cr (zolpidem tartrate) tablet, coated. Daily Med. <http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=5420>

<sup>5</sup> Benzodiazepines. Center for Substance Abuse Research – UMD. <http://www.cesar.umd.edu/cesar/drugs/benzos.asp>

<sup>6</sup> Ambien cr (zolpidem tartrate) tablet, coated. Daily Med. <http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=5420>

<sup>7</sup> R M Cysneiros, et. al. Pharmacokinetic and Pharmacodynamic Interactions Between Zolpidem and Caffeine. *Clinical Pharmacology & Therapeutics*. <http://www.nature.com/clpt/journal/v82/n1/abs/6100211a.html>

<sup>8</sup> Cupp, Melanie Johns. Cytochrome P450: New Nomenclature and Clinical Implications. *American Family Physician*. <http://www.aafp.org/afp/980101ap/cupp.html>

<sup>9</sup> R M Cysneiros, et. al. Pharmacokinetic and Pharmacodynamic Interactions Between Zolpidem and Caffeine. *Clinical Pharmacology & Therapeutics*. <http://www.nature.com/clpt/journal/v82/n1/abs/6100211a.html>

<sup>10</sup> Moon, Ho-Jin. Effects of chromosomal variations on pharmacokinetic activity of zolpidem in healthy volunteers: An array-based comparative genomic hybridization study. *Biochemical and Biophysical Research Communications*. Volume 356, Issue 4, 18 May 2007, Pages 981-987.

<sup>11</sup> Kralic, J.E. GABAA receptor alpha-1 subunit deletion alters receptor subtype assembly, pharmacological and behavioral responses to benzodiazepines and zolpidem. 43 (2002) 685–694. *Neuropharmacology*.

<sup>12</sup> Ambien cr (zolpidem tartrate) tablet, coated. Daily Med. <http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=5420>

<sup>13</sup> R M Cysneiros, et. al. Pharmacokinetic and Pharmacodynamic Interactions Between Zolpidem and Caffeine. *Clinical Pharmacology & Therapeutics*. <http://www.nature.com/clpt/journal/v82/n1/abs/6100211a.html>

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<sup>14</sup> Inomata, Shinichi. Pharmacogenetics and Genomics. *Clinical Pharmacology & Therapeutics* (2005) 78, 647–655; doi: 10.1016/j.clpt.2005.08.020