# Polypharmacology Induces "Sleep Driving"

*This case study illustrates the role of toxicological weight-of-evidence (WOE) in a motor vehicle accident case involving multiple pharmaceuticals. It also illustrates how drug interactions can be considered evidential in a toxicological causation assessment.*

On the evening prior to a serious motor vehicle accident, a woman who failed to stop at a red light was given a citation by a police officer and then escorted home. The woman ingested Xanax and Ambien just before bed. Upon experiencing difficulty breathing the next morning, she called her physician and was told to come to his office immediately. After dressing, she then ingested a dose of Prozac. While driving to the physician's office, she ran a stop sign and collided with another vehicle.

The police officer who arrived at the accident scene suspected a possible drug influence when he saw her taking medicine bottles from her purse and noticed other bottles of medication on the seat. When questioned, the woman did not seem to recognize where she was or what was happening.

After transport to the hospital for treatment, the woman was released but returned an hour later and remained for two days for treatment of asthmatic complications. The driver of the other vehicle subsequently filed a personal injury lawsuit. Dr Sawyer was retained to conduct an objective toxicological assessment.

Multiple pharmaceutical interactions carry an imprecise risk of driving impairment.[a]

## Pharmaceutical Exposure Assessment

Dr. Sawyer reviewed the police reports, the woman's deposition testimony and her medical history which was significant for treatment of depression and anxiety. She had also been diagnosed with asthma, fibromyalgia, anemia and hypertension. The records revealed that the woman had a history of losing consciousness due to her asthma.

Dr. Sawyer performed a thorough review of the various pharmaceuticals that had been prescribed. Meanwhile, the forensic toxicology laboratory had conducted an independent analysis of her blood taken just after the accident. From this, Dr. Sawyer assembled a table comparing the reported blood levels with the therapeutic and toxic levels for each substance detected in the lab report.

### Adverse Effects of Antidepressants

Dr. Sawyer noted in his clinical toxicology analyses that three (3) prescription antidepressants detected in the lab report posed significant, well-established toxicological effects and documented interaction issues. As several of the drugs had been administered for similar purposes, their presence encompassed the realm of polypharmacology which is defined as "the treatment of diseases by modulating more than one target." Polypharmacology can encompass both one drug binding to multiple targets and multiple drugs binding to different targets. Dr. Sawyer noted the following points for each medication:

Drug interactions can induce profound toxicological effects.[c]

### Ambien (zolpidem)[1]

- Side effects include drowsiness, dizziness, diarrhea and a "drugged feeling." Central nervous system effects include impairment of alertness and motor coordination. The manufacturer cautions that Ambien *should not be taken with other medicines that can cause drowsiness.*
- Abnormal thinking, behavior changes and *complex behaviors such as "sleep driving"* (i.e. driving while not fully awake after ingestion of a sedative-hypnotic with amnesia for the event) have been reported with Ambien.
- The FDA/manufacturer's package insert cautioned that *potential impairment may occur the day following ingestion of Ambien.*

### Prozac (fluoxetine)[2]

- Potential for cognitive and motor impairment has been reported. Prozac has the potential to impair judgment, thinking and motor skills. Caution is advised when operating machinery *including motor vehicles* (generally includes warnings and follow-up by the prescribing physician to be certain the patient is tolerating the medication without significant side effects).
- Drug interactions: Co-administration of Xanax (alprazolam) has resulted in *increased alprazolam plasma concentrations* and in further psychomotor performance decrement due to increased alprazolam levels.
- Other adverse effects of the central nervous system: insomnia, nervousness, anxiety, somnolence, dizziness, tremor, *abnormal thinking.*

### Xanax (alprazolam)

- Adverse effects of the central nervous system include: drowsiness, light-headedness, confusion, nervousness and dizziness. Because this drug may cause dizziness or drowsiness, users *should not drive or operate machinery or engage in any activity requiring alertness* (generally requires tolerance and follow-up by the prescribing physician to be certain the patient is tolerating the medication without significant side effects).
- Serious side effects include: unusual risk-taking behavior, decreased inhibitions, *no fear of danger,* feeling light-headed and fainting.
- Co-administration of Prozac with Xanax is contraindicated *due to potentiated increase of Xanax maximum plasma concentration.*
- Benzodiazepines (including Xanax) produce *additive effects* to the central nervous system when co-administered with other drugs which produce central nervous system depression.

## Summary of Results

Dr. Sawyer applied an objective weight-of-evidence (WOE) methodology to the exposure factors. By charting a timeline with respect to measured blood levels, deposition testimony and the therapeutic and toxic blood concentrations documented in the peer-reviewed toxicological literature, he identified specific, predictable polypharmacological effects:

- At 0.151 ug/ml the Xanax blood level was **clearly in the toxic range.** This high level was achieved through drug interaction producing an equivalent Xanax ingestion of 13.3 mg (approximately 6.7 tablets),[3] resulting in *substantial impairment.*
- The Prozac blood level was at the **extreme end** of the therapeutic range at 0.494 ug/ml. Prozac is also known to increase the toxicity of Xanax. Calculations showed that the Prozac/Xanax interaction decreased clearance by 21%, enhanced the maximum plasma concentration by 46% and increased half-life by 17%. The symptomatic result of this enhancement was *significantly decreased psychomotor performance.*
- The Ambien blood level was also at the **extreme end** of the therapeutic range at 0.146 ug/ml and is consistent with dosage 1 to 2 hours prior to the accident. Ambien is *known to induce "sleep driving"* and (like Prozac) can increase the toxicity of Xanax.

**Therapeutic and Toxic Levels of Drugs Compared to Measured Blood Levels**

| Drug Name (generic) | Normal Therapeutic Level (ug/ml) | Toxic Level (ug/ml) | Measured Blood Level (ug/ml) |
|---|---|---|---|
| Ambien (zolpidem) | 0.08 to 0.15 [a]<br>0.03 to 0.2 [b] | 0.5 [a]<br>0.5 [b] | **0.146** [c] |
| Prozac (fluoxetine) | 0.16 to 0.5 [a]<br>0.1 to 0.5 [b] | >0.5<br>>0.5 | **0.494** |
| Xanax (alprazolam) | 0.005 to 0.05 [a]<br>0.01 to 0.05 [b] | 0.1 to 0.4 [a]<br>0.075 [b] | **0.151** [d] |

a. Schulz, M., et al., "Therapeutic and toxic blood concentrations of more than 500 drugs," 1997, Pharmazie Vol. 52, pages 895-911.

b. Repetto, MR., et al., "Habitual toxic and lethal concentrations of 103 drugs of abuse in humans," 1997, Clinical Toxicology, Vol. 35(1), pages 1-9.

c. High-end of the therapeutic range consistent with peak absorption level occurring 1 to 2 hours post-dosage.

d. Subject was prescribed a 2 mg dose of Xanax. For comparison, 9 mg of Xanax produces a blood level of 0.102 ug/ml; subject's blood level of 0.151 ug/ml is equivalent to a dose of 13.3 mg or 6.7 tablets.

Demonstrative Illustrating "Therapeutic and Toxic Levels of Drugs Compared to Subject's Measured Blood Levels."[(b)]

## Outcome

Dr. Sawyer was able to present compelling evidence to reasonable toxicological certainty that the additive effects of the pharmaceutical interactions, the self-administered doses and the times at which they were taken substantially contributed to predictable impairment at the time of the accident. His report was subsequently instrumental in a rapid settlement favorable to plaintiff.

*(Disclaimer: Toxicology case studies are impartial and objective summaries of toxicological matters in which TCAS was retained for the purpose of assessing health-based factors which, in some cases, led to a determination of causation. No names or identifying information have been provided due to privacy and legal considerations. In the above matter, Dr. Sawyer was retained by plaintiff.)*

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**Notes and References**


1. Adverse effects per "2011 Physicians' Desk Reference," Edition 65, pages 2924-2929
2. Adverse effects per "2011 Physicians' Desk Reference," Edition 65, pages 1816-1827
3. Baselt, RC, "Disposition of toxic drugs and chemicals in man," 6th edition, Biomedical Publications, page 33.


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**Images**

a. Photo by Chris Chidsey, Marlborough, Wiltshire
b. *TCAS* report demonstrative (redacted), graphical image © Copyright 2017 TCAS, LLC.
c. Photo by Chief Jason Loper, Fairview Township Police Department

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**A Message from Dr. William R. Sawyer**
**Chief Toxicologist, *TCAS, LLC***

*"Dose and temporal relationships are critical factors in a causative assessment. Pharmacological interactions must be identified and quantified to establish an assessment outcome to reasonable toxicological certainty."*




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