CNS Depressants and Antidepressants

Pamela E. Potter, Ph.D.
Dept. Pharmacology
Midwestern University
Arizona College of Osteopathic Medicine

CNS Depressants

- Alcohol
- Opium
- Bromides - 1800s
- Chlortal hydrate - 1800s
- Barbiturates - 1912-1950s
- Benzodiazepines - 1961
- Zolpidem (Ambien), zalpelon (Sonata) - 1990s-2000s
Drugs and the GABA<sub>A</sub> Receptor

- Barbiturates
  - Increase **duration** of action of GABA
  - Independently opens Cl⁻ channel
  - Inhibits other excitatory receptors
  - Very low margin of safety
  - Low therapeutic index (LD<sub>50</sub> vs TD<sub>50</sub>)
Effects

- Diminish awareness
- Decrease response to stimulation
- Decrease cognition
- Decrease activity
- Drowsiness, lethargy
- Amnesia
- Hypnosis

Side Effects

- CNS depression
- respiratory depression!
- dangerous when combined with alcohol
- physical dependence
- severe withdrawal
Overdose can be Fatal!

Benzodiazepines

- Very commonly prescribed in 1960s (housewife’s friend)
- Anxiolytic - immediate, effective
- Sedative-hypnotic
- Anticonvulsant
- Intensify the action of GABA - very safe, even in overdose
Rise and fall in the use of benzodiazepines between 1965 and 1985

Benzodiazepines Facilitate GABA
Barbiturates Potentiate GABA

Dose- Effect Relationships
Half-lives (hrs)

- Diazepam: 43 (30-60)
- Chlordiazepoxide: 15-40
- Nordiazepam: 40-100
- Lorazepam (Ativan): 14
- Oxazepam (Serax): 8
- Alprozolam (Xanax): 12

- The sedative/anticonvulsant action of diazepam is shorter than its other effects
- Time to peak effect of lorazepam ranges from 1-6 hrs

Cimetidine Inhibition of Benzodiazepine Metabolism

[Graph showing plasma concentration of midazolam over time with and without cimetidine]
Erythromycin Decreases Metabolism of Midazolam

The effects are supra-additive, i.e., the effects of two together are greater than the sum of the two alone.

Benzodiazepines can produce physical and psychological dependence.
Zolpidem (Ambien)

- Binds to benzodiazepine receptor subtype **BZ1**
- **VERY rapid action; “blackouts”**
- Little effect on REM sleep
- Approved for short-term treatment of insomnia
- Zalpelon (Sonata) similar

Antihistamines

- Diphenhydramine (Benadryl)
- Chlorpheneramine (Chlor-Trimeton)
- Dimenhydrinate (Dramamine)
- Block H1 receptor
- Very sedating until tolerance develops
Tolerance - Antihistamines


Benzodiazepine Tolerance

Chlordiazepoxide

Diazepam

Tolerance to Pentobarbital

Benzodiazepines cause tolerance to EtOH

**Tolerance - Alcohol**

Carisoprodol (Soma) is a sedating muscle relaxant, in a group that also includes:
- cyclobenzaprine (Flexeril), metaxolone (Skelaxin), methocarbamol (Robaxin)
- These act as sedatives in the brain stem
- Carisprodol is converted to meprobamate (Milltown), which acts like a barbiturate
- Now a very popular drug of abuse
Conversion of Carisoprodol to Meprobamate

Mean carisoprodol and meprobamate serum concentration in the blood sample taken before carisoprodol administration (0) and in samples collected 40, 80, and 125 minutes after administration. Error bars indicate ± 1 SE.
CNS Depressants and Driving

- At any time, about 5% of people are taking prescribed benzodiazepines.
- In drivers apprehended for impaired driving, 10-15% will have benzodiazepines in their blood.
- The effect of benzodiazepines on driving performance is variable and not always easy to predict.

CNS Depressants/Driving

- Diazepam, flunitrazepam and clonazepam seem to be the most common drugs reported in drivers suspected to be impaired.

Drug Alcohol Depend. 47, 125-136 (1997)
Australian study showed that drivers with benzodiazepines in their blood were somewhat more likely (O.R. 4.5 vs 3.2) to cause a car accident. Those with BAC > 0.5% had an O.R. of 34.1. The odds of having an accident if psychotropic drugs were combined with alcohol was increased 1.7 times.

Austrian study of drivers injured in car accidents found:
- 36.9% had BAC = .149 ± .054
- 8.1% of drivers had benzodiazepines, average drug level 68.7± 62.6 mcg/l
- Another study found vigilance impaired after single dose of 5 and 10 mg diazepam, 0.5 mg alprazolam, but not 10 mg oxazepam.
CNS Depressants & Car Accidents

5-year study showed elderly people taking benzodiazepines (Medicaid records) 2-4 times more likely to cause an automobile accident at higher doses of diazepam (≥ 20 mg/day)

- At low doses, likelihood of accident no higher than non-drug control
- TCAs (e.g. 125 mg amitriptyline) increased likelihood 5-6 times

Table 6: New users cohort. Logistic regression models risk for hospitalization for injury due to traffic accidents by individual BZD use, stratified for age.

<table>
<thead>
<tr>
<th>Independent variables</th>
<th>OR (CI)</th>
<th>OR (CI)</th>
<th>OR (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All ages</td>
<td>OR</td>
<td>OR</td>
<td>OR</td>
</tr>
<tr>
<td>Triazolam use (S)</td>
<td>3.2*</td>
<td>1.4-7.3</td>
<td>3.5*</td>
</tr>
<tr>
<td>Flurazepam use (L)</td>
<td>5.1*</td>
<td>2.3-11.6</td>
<td>6.1*</td>
</tr>
<tr>
<td>Lorazepam use (S)</td>
<td>2.4*</td>
<td>1.0-6.3</td>
<td>2.1</td>
</tr>
<tr>
<td>Diazepam use (L)</td>
<td>3.1*</td>
<td>1.4-6.5</td>
<td>3.0*</td>
</tr>
<tr>
<td>Oxazepam (S)</td>
<td>1.0</td>
<td>0.3-3.7</td>
<td>1.3</td>
</tr>
</tbody>
</table>
1 mg alprozolam (Zanax) given 1 hour before the driving test, compared with placebo  Neuropsychopharmacology 27, 260-269 (2002)
Zolpidem Impairs Driving

**TABLE 1. Mean ± SD of performance parameters (See text for abbreviations)**

<table>
<thead>
<tr>
<th>Variable</th>
<th>PLAE</th>
<th>ETA</th>
<th>PLAC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Driving Performance</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SDLP (cm)</td>
<td>17.6 ± 4.2</td>
<td>18.6 ± 4.1</td>
<td>17.5 ± 4.2</td>
</tr>
<tr>
<td>SDS (km/h)</td>
<td>2.62 ± 0.07</td>
<td>2.53 ± 0.71</td>
<td>2.25 ± 0.07</td>
</tr>
</tbody>
</table>

**EtOH was administered to produce BAC 0.05% on Day 1. Zolpidem or Zapelon were administered during the night, and driving was measured 6 hours later (in the morning)**

**Triazolam compares to EtOH at producing impairment**

**Alcohol breath measure was 0.13% at time of testing**
## Benzodiazepines

<table>
<thead>
<tr>
<th>Drug</th>
<th>Driving Impaired</th>
<th>Therapeutic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flurazepam</td>
<td>15 mg</td>
<td>15 mg, bedtime</td>
</tr>
<tr>
<td>Flunitrazepam</td>
<td>1 mg</td>
<td>-----</td>
</tr>
<tr>
<td>Temazepam</td>
<td>&gt; 20 mg</td>
<td>15 mg</td>
</tr>
<tr>
<td>Triazolam</td>
<td>0.5 mg</td>
<td>0.25 mg</td>
</tr>
<tr>
<td>Oxazepam</td>
<td>10-50 mg</td>
<td>10-15 mg</td>
</tr>
<tr>
<td>Diazepam</td>
<td>5 mg t.i.d.</td>
<td>2-10 mg</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>0.5 mg</td>
<td>2-3 mg</td>
</tr>
</tbody>
</table>


### Drug Detection

![Drug Detection Graph](Link to image)

## Concentrations Producing Impairment

Table 3: Analytical findings: concentrations of drug found (ng/ml) in the studied sample (n = 211) and their relationship with the physicians conclusion on CTD.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Not Impaired (N = 15%) (mean (SD))</th>
<th>Impaired (N = 65%) (mean (SD))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diazepam (n = 411)</td>
<td>302 (322)</td>
<td>467 (436)</td>
</tr>
<tr>
<td>Oxazepam (n = 73)</td>
<td>943 (786)</td>
<td>1849 (1502)</td>
</tr>
<tr>
<td>Flunitrazepam (n = 211)</td>
<td>13 (13)</td>
<td>198 (10)</td>
</tr>
<tr>
<td>Nitrazepam (n = 29)</td>
<td>111 (58)</td>
<td>225 (183)</td>
</tr>
<tr>
<td>Alprazolam (n = 11)</td>
<td>46 (40)</td>
<td>151 (93)</td>
</tr>
<tr>
<td>Triazolam (n = 29)</td>
<td>7 (7)</td>
<td>7 (3)</td>
</tr>
<tr>
<td>Chlordiazep (n = 55)</td>
<td>85 (129)</td>
<td>79 (98)</td>
</tr>
</tbody>
</table>

* Results based on Mann–Whitney test.

\( a \) P < 0.001.

\( b \) P < 0.001.

---

![Image](image.png)


**% of cases determined "not impaired"**

- **Therapeutic**
- **Mildly elevated**
- **Moderately elevated**
- **Highly elevated**

**Level of benzodiazepine and BAC grouped**

**Benzodiazepine**

**Reference group with alcohol**
### Other Drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose: Driving Impaired</th>
<th>Therapeutic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Secobarbital</td>
<td>200 mg</td>
<td>100-200 mg</td>
</tr>
<tr>
<td>Buspirone</td>
<td>10 mg, t.i.d.</td>
<td>10 mg</td>
</tr>
<tr>
<td>Zolpidem</td>
<td>&gt; 10 mg</td>
<td>5-10 mg</td>
</tr>
<tr>
<td>Zalpelon</td>
<td>&gt; 20 mg</td>
<td>5-10 mg</td>
</tr>
<tr>
<td>Diphenhydramine</td>
<td>50 mg</td>
<td>50 mg</td>
</tr>
<tr>
<td>Loratadine (Claritin)</td>
<td>20 mg</td>
<td>10 mg</td>
</tr>
<tr>
<td>Carisoprodol</td>
<td>----</td>
<td>400 mg, t.i.d.</td>
</tr>
</tbody>
</table>


---

### Antidepressants

- Ready to be happy?
- Wash Your Blues Away!
Depression

- One of most common mental illnesses (10-25%)
- Symptoms:
  - Depressed mood
  - Diminished interest
  - Weight/appetite change
  - Insomnia/hypersomnia, Fatigue
  - Worthlessness, Indecisiveness
  - Suicidal thoughts

Noradrenergic Pathways

Locus ceruleus projections

Dorsal adrenergic bundle

Locus Ceruleus

spinal cord
Norepinephrine

- Mood: antidepressants affect NE
- May be involved in anxiety
- Pain regulation
- Learning and memory
- Stress depletes NE
- Alpha and beta receptors
- Drugs act on synthesis, uptake and breakdown

Serotonin Pathways

- Raphe Projects throughout the cortex
- Raphe Nuclei
- Spinal cord
Serotonin

- Mood
  - depression treated with 5HT re-uptake inhibitors
- May promote sleep (tryptophan)
- Anxiety
- Obsessive compulsive disorder
- Hunger or appetite
- Perception (LSD)
- Many receptor subtypes, targeted by newer drugs

The Amine Hypothesis
PET Scans

Treatments for Depression

- Tricyclic Antidepressants
- Monoamine Oxidase Inhibitors
- Selective Serotonin Reuptake Inhibitors (SSRIs)
- "Newer" antidepressants
- Electroconvulsive therapy
Tricyclic Antidepressants

- Inhibit re-uptake of NE and 5HT
- Anticholinergic/Antihistamine
- Sedation, often significant
- No euphoria/low abuse potential
- 2-3 weeks to have effect
TCA Metabolism

More sedating/anticholinergic

Less sedating/anticholinergic

CNS
- Sedation
- Memory/cognition
- Analgesia

Periphery
- Cardiac depression/irritability
- Torsades de pointes
- alpha1 blockade, postural hypotension
**TCA Uses**

- Depression
  - 2-3 weeks for effect
  - Side effects and potential toxicity limits use
- Panic disorder
- **Chronic pain**, headache
  - Very low doses
- Fibromyalgia
- Enuresis

**Side Effects**

- Blurred vision, Dry mouth
- Tachycardia
- Constipation, Urinary retention
- Orthostatic hypotension
- Sinus tachycardia
- Weight gain
- Sedation
Monoamine Oxidase Inhibitors

- Irreversibly inhibit MAO-A, which breaks down NE & 5HT, and MAO-B, which breaks down DA
- Used for depression which doesn’t respond to other drugs, atypical depression, etc...
  - Phenelzine (Nardil)
  - Tranylcypromine (Parnate)

Side Effects

- Severe hypertensive crisis!
  - MAO in the gut breaks down certain amines as we eat them, such as tyramine
  - Tyramine causes release of NE
  - Tyramine in foods: red wine, beer, aged cheese, etc...
- Sympathomimetics (cold medicines) also cause HTx with MAOIs
Side Effects

- Tremors
- Sedation, excitation, insomnia
- Orthostatic hypotension
- Delayed ejaculation
- Fatigue
- Weight gain, skin rash
- Dizziness, blurred vision, constipation

SSRIs

- Inhibit re-uptake of 5-HT
  - Fluoxetine (Prozac)
  - Sertraline (Zoloft)
  - Fluvoxamine (Luvox)
  - Paroxetine (Paxil)
  - Citalopram (Celexa)
  - Escitalopram (Lexapro)
- Inhibit NE & 5-HT re-uptake
  - Venlafaxine (Effexor)
SSRIs

- **Fluoxetine**
  - Prozac, Prozac Weekly, generic
  - Serafem (14 days before menses)
  - Antidepressant effect usually takes 3-4 weeks to develop

  - Antidepressants are NOT mood altering drugs, they do NOT cause euphoria
Fluoxetine Metabolism

\[
\text{Fluoxetine} \rightarrow \text{Norfluoxetine}
\]

Pharmacokinetics - Fluoxetine

- Slow onset of effect
- Late side effects
- Long duration after drug discontinued
- Half-life of 4.7 and 16.7 for fluoxetine and norfluoxetine after 3-6 mos administration

Drug Interactions

- Fluoxetine inhibits CYP2D6
- Increases levels of tricyclic antidepressants (clearance dec. 70% or more)
- Toxicity may occur with TCAs if combined with fluoxetine
- CYP2D6 inhibition interferes with conversion of some opioids to active compounds

Paroxetine (Paxil)

- Shorter half-life and shorter duration of action than fluoxetine
- Less effect on most hepatic enzymes (except CYP2D6), fewer drug interactions
- More selective than fluoxetine for 5-HT uptake
- More likely to cause sedation
### Pharmacokinetics

<table>
<thead>
<tr>
<th>DRUG</th>
<th>Usual Dose (mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paroxetine</td>
<td>20-40</td>
</tr>
<tr>
<td>Sertraline</td>
<td>100-150</td>
</tr>
<tr>
<td>Citalopram</td>
<td>20-40</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>10-20</td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td>100-200</td>
</tr>
</tbody>
</table>

### Pharmacokinetics

<table>
<thead>
<tr>
<th>DRUG</th>
<th>$t_{1/2}$ (hr)</th>
<th>Conc. (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paroxetine</td>
<td>22</td>
<td>30-100</td>
</tr>
<tr>
<td>Sertraline</td>
<td>24 (65)</td>
<td>25-50</td>
</tr>
<tr>
<td>Citalopram</td>
<td>36</td>
<td>75-150</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>30 (59)</td>
<td>--</td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td>15-20</td>
<td>100-200</td>
</tr>
</tbody>
</table>
**Heterocyclic Antidepressants**

**Venlafaxine (Effexor)**

- Blocks both 5-HT and NE re-uptake
- Long duration of action
- Side effects common
- Increases blood pressure in some patients
Antidepressant Trends

Figure 1. Use of Older and Newer Antidepressants in Adult Primary Care Visits

- Older agents include tricyclic and tetracyclic antidepressants, tricyclic and tetracyclic antidepressant combination products, monoamine oxidase inhibitors, and trazodone.
- Newer agents include selective serotonin reuptake inhibitors, bupropion, mirtazapine, nefazodone, and venlafaxine.


Uses of SSRIs

- Depression - very effective
- Panic disorder
- Obsessive-compulsive disorder
- Bulimia
- PMDD
- Alcoholism- recovery
- Premature ejaculation
**Side Effects**

- Mild: no cardiac toxicity
- GI: nausea, loss of appetite
- Weight loss or gain
- CNS: anxiety, insomnia, or sedation
- Sexual disinterest/dysfunction
- Photosensitivity

**Serotonin Syndrome**

- With MAOIs
- Agitation, confusion, delirium
- Hyperpyrexia, shivering
- Diaphoresis, diarrhea, hyperreflexia, tremor
- May progress to convulsions and coma
Discontinuation Symptoms

- Rare, may last 5-8 days
  - dizziness, ataxia, parasthesias
  - flu-like symptoms, sleep disturbances
  - anxiety, agitation, crying spells, irritability.
  - most common with short acting drugs, e.g. paroxetine

Mirtazapine (Remeron)

- NOT an uptake inhibitor
  - blocks presynaptic $\alpha_2$ receptors
  - blocks $5-HT_{2A}$ and $5-HT_3$ receptors
  - Reduces anxiety, insomnia, nausea, sexual problems
- Antihistamine – significant sedation
- Effects similar to TCAs, without cardiac toxicity
Mirtazapine Sedation

![Bar graph showing LARS sedation, mean maximum change from baseline ± SEM on Day 2, *p>0.05](image)

Bupropion (Wellbutrin)

- **Inhibits DA re-uptake**
  - (Zyban)- extended release, smoking cessation

- **Side Effects**
  - CNS stimulation, anxiety, but not sedating
  - May cause seizures (esp with TCAs)
  - May work where others haven’t
  - Few sexual side effects

Antidepressant Trends

Driving Impairment

- Elderly drivers taking TCAs about 2x more likely to be involved in an accident*
- Studies using standard driving tests designed to investigate antidepressant effects
- Driving 62 mi on a highway at 59 mph and a steady lateral position
- SDLP measured

**SDLP**

- SDLP rises exponentially as BAC rises
- BAC over 0.5 mg/ml correlates with increased fatal accidents
- BAC of 0.5 mg/ml causes a 2.4 cm. change in SDLP
- Test other drugs against this criteria

**TCAs and driving**

- Meta analysis of 10 studies
- Acute doses of
  - Amitriptyline, 75 mg
  - Doxepin, 75 mg
  - Imipramine, 50 mg
- Caused changes in SDLP equivalent to BAC 0.8 mg/ml
- BUT after 1 week treatment tolerance had developed to the effect

TCAs and Driving


SSRIs and Driving

- Fluoxetine and paroxetine (SSRIs) considered non-sedating, have never been shown to affect driving
- Venlafaxine also does not affect driving
- Nefazodone has some effect, but tolerance develops rapidly
SSRIs and Driving


Mirtazapine increases reaction time

**Fluoxetine/ BDZs**

*Figure 4. Mean ± SE ΔSLEEP for patients receiving concomitant treatment during 6 weeks of treatment with Fluoxetine.*

- FLU 20 mg qd: 20 mg qd
- FLU 20 mg qd: Comp BDZ
- FLU 20 mg qd: Inc BDZ

BAC 0.8 mg/ml


---

**Somnolence/ Driving**

*Figure 5. Antidepressants recommended to be given over the day.*

A. Antidepressants Recommended to Be Given Over the Day

\[ \Delta SLEEP = -1.23 + 0.14 \times \text{Somnolence} \]

\[ r = 0.95 \]

Equivalent effect of BAC=0.5 mg/ml

Summary

- TCAs can significantly impair driving, especially if combined with alcohol
- SSRIs in general do not affect driving ability - but might increase the effects of BDZs or alcohol
- Mirtazapine causes somnolence, but driving studies have not been done
- There are no studies for bupropion, although impairment is highly unlikely