A Horse of a Different Color: How Formulation Influences Medication Effects

(page 137 in syllabus)

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University of Florida
CEO and Medical Director, Florida Clinical Research Center, LLC

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Learning Objectives

• Identify medications for which differences in formulation could influence therapeutic effects
• Differentiate the FDA definitions of bioequivalence and therapeutic equivalence
• Identify medications for which generic substitution is consistent with best practices
A patient with bipolar disorder and alcohol abuse is being prescribed a controlled-release medication with a narrow therapeutic index, and his clinician wants to select a formulation that minimizes the risk of dose dumping. Which of the following formulations might be the best choice?

1. Controlled-release single-unit hydrophilic matrix
2. Controlled-release single-unit hydrophobic matrix
3. Controlled release osmotic reservoir
How Formulation Influences Medication Effects: Pharmacokinetics

- Absorption
- Distribution
- Elimination

Onset of action
Consistency of plasma levels
Duration of action
Ability to cross blood-brain barrier
Parent drug/active metabolites

Ideal Drug Delivery

- **Plasma Concentration**
- **Time**
- **Toxic Level**
- **Desired Effect**

- **Start of Treatment**
- **End of Treatment**


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Formulation Effects on Plasma Concentration

Case in Point: Methylphenidate PK Patterns of Time-Release Beads vs OROS

Modified-Release Formulations
Modified-Release Formulations

- Deliver drugs in a controlled and predictable manner over time or in a predetermined position in GI tract
  - Delayed release
  - Extended release
  - Pulsatile release
  - Chrono-release
  - Targeted delivery
  - Combination of immediate, delayed, and/or extended

- Fundamental properties
  - Drug-release course
  - Dissolution profile
Modified-Release Formulations

• Mechanisms
  – Matrix vs reservoir
  – Single-unit vs multiparticulate

• Differentiating factors
  – Transit time in GI tract
  – Location of drug released
  – Dissolution of active molecule
  – Permeation through GI membrane
  – First-pass clearance
  – Intestinal degradation
Modified-Release Technologies: Matrix System

- Polymeric matrix
- Drug

Matrix swelling

Matrix degradation

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Modified-Release Technologies: Matrix System

• Hydrophilic
  – Most common, especially for poorly soluble drugs
  – Release can be affected by food/alcohol
  – Requires large amount of excipient, so dose loading is low

• Hydrophobic
  – For water-soluble drugs
  – Greater physical stability than hydrophilic
  – Tablet becomes inert in presence of water/GI fluid
Modified-Release Technologies: Reservoir System

coating

polymeric membrane

drug

inner core
Coating

- Differences in drug release depending on type of coating
  - Insoluble
  - pH dependent
  - Slowly erodible
Osmotic Controlled-Release Oral Delivery System (OROS)

- **coating**: drug, binders
- **semipermeable rigid membrane**
- **third compartment**: molecules that react with water
- **second compartment**: high concentration of drug
- **first compartment**: low concentration of drug
- **opening**

Stahl, Mignon. Stahl's Illustrated Attention Deficit Hyperactivity Disorder 2009. Copyright © 2011 Neuroscience Education Institute. All rights reserved.
Modified-Release Technologies:
Single-Unit vs Multiparticulate Pellet Systems

- Advantages of multiparticulate
  - Less dependent on gastric emptying rate
  - Less subject variability in GI transit time/dietary state
  - Less local irritation
  - Less risk of dose dumping
  - More flexibility for complex release
Multiparticulate System: Multiple Bead System

gelatin capsule

two different types of beads (one delayed, one immediate)

drug

Stahl, Mignon. Stahl's Illustrated Attention Deficit Hyperactivity Disorder 2009.
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Modified-Release Technologies: Effect of Food

- Single-unit affected more than multiparticulate
- Hydrophilic matrix affected more than other matrix systems
- Osmotic systems not heavily affected
Modified-Release Oral Formulations

Advantages
- Stable plasma concentrations
- Potentially fewer side effects
- Less frequent dosing/ better adherence

Disadvantages
- Cannot crush/chew
- Cannot mix with food (exception: beads)
- Potential for inter- and intraindividual variability
# Oral Modified-Release Antidepressants

<table>
<thead>
<tr>
<th>Formulation*</th>
<th>Delivery</th>
<th>Profile</th>
</tr>
</thead>
<tbody>
<tr>
<td>bupropion SR</td>
<td>Matrix tablet</td>
<td>Twice-daily dosing; reduces seizures compared to IR</td>
</tr>
<tr>
<td>bupropion XL</td>
<td>Reservoir tablet, diffusion through coating</td>
<td>Once-daily dosing; reduces seizures compared to IR; reduces risk of dose-dumping</td>
</tr>
<tr>
<td>bupropion hydrobromide ER</td>
<td>Film-coated tablet</td>
<td>Once-daily dosing; allows single administration of 450 mg equivalency to bupropion hydrochloride salt</td>
</tr>
<tr>
<td>desvenlafaxine ER</td>
<td>Matrix tablet; pH dependent</td>
<td>Once-daily dosing</td>
</tr>
<tr>
<td>fluoxetine weekly</td>
<td>Capsule with enteric-coated pellets; pH dependent (&gt;5.5)</td>
<td>Once-weekly dosing; pellets dissolve after they reach portion of GI tract where pH exceeds 5.5</td>
</tr>
</tbody>
</table>

*Generic formulations may use different delivery technologies.*

*Additional information was taken from drug inserts, company Web sites, and FDA Web site.*
Oral Modified-Release Antidepressants

<table>
<thead>
<tr>
<th>Formulation*</th>
<th>Delivery</th>
<th>Profile</th>
</tr>
</thead>
<tbody>
<tr>
<td>fluvoxamine CR</td>
<td>Multiparticulate SODAS capsule</td>
<td>May be better tolerated than IR, particularly with less sedation</td>
</tr>
<tr>
<td>paroxetine CR</td>
<td>Degradable matrix tablet; enteric film-coated</td>
<td>Delayed release until tablet has passed through stomach; 20% of drug remains in tablet</td>
</tr>
<tr>
<td>trazodone ER</td>
<td>Matrix tablet with membrane that gels in aqueous solution, protecting controlled release properties</td>
<td>Once-daily dosing; can maintain controlled release property if split; reduces risk of dose dumping</td>
</tr>
<tr>
<td>venlafaxine XR</td>
<td>Multiparticulate; diffusion through coating membrane on spheroids; not pH dependent</td>
<td>Once-daily dosing; reduces side effects compared to IR</td>
</tr>
</tbody>
</table>

*Generic formulations may use different delivery technologies.

Additional information was taken from drug inserts, company Web sites, and FDA Web site.
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## Oral Modified-Release Amphetamines

<table>
<thead>
<tr>
<th>Formulation/Delivery</th>
<th>Delivery</th>
<th>Profile</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sustained-release d-amphetamine</td>
<td>Spansule capsule</td>
<td>No lunch dosing; low risk for insomnia unless dosed at night</td>
</tr>
<tr>
<td>Extended-release d,l-amphetamine</td>
<td>Multiparticulate capsule containing coated beads, some IR and some delayed</td>
<td>Continued effects into early evening</td>
</tr>
</tbody>
</table>

## Oral Modified-Release Methylphenidates

<table>
<thead>
<tr>
<th>Formulation/Delivery</th>
<th>Delivery</th>
<th>Profile</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sustained-release racemic</td>
<td>Wax matrix tablet</td>
<td>Lunch dosing may be needed; low risk for insomnia unless dosed at night</td>
</tr>
<tr>
<td>Time-release beads racemic</td>
<td>Multiparticulate capsule</td>
<td>Less risk for insomnia than OROS</td>
</tr>
<tr>
<td>SODAS microbeads racemic MPH-XR</td>
<td>Multiparticulate capsule; half of beads are IR, half are delayed release</td>
<td>Less risk for insomnia than OROS</td>
</tr>
<tr>
<td>OROS racemic</td>
<td>Osmotic reservoir</td>
<td>Continued effects into evening</td>
</tr>
<tr>
<td>SODAS microbeads d-methylphenidate XR</td>
<td>Multiparticulate capsule; half of beads are IR, half are delayed release</td>
<td>Once-daily dose in the morning</td>
</tr>
</tbody>
</table>

**ORS =** osmotic controlled-release oral delivery system  
**SODAS =** spheroidal oral drug absorption system

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Additional information was taken from drug inserts, drug company Web sites, and the FDA Web site.
## Oral Modified-Release Psychotropics

<table>
<thead>
<tr>
<th>Formulation*</th>
<th>Delivery</th>
<th>Profile</th>
</tr>
</thead>
<tbody>
<tr>
<td>alprazolam XR</td>
<td>Hydrophilic matrix tablet</td>
<td>Once-daily; can allow for more sustained effect with less breakthrough anxiety</td>
</tr>
<tr>
<td>carbamazepine ER</td>
<td>Osmotic reservoir tablet 3-bead capsule</td>
<td>Can reduce sedation and other side effects</td>
</tr>
<tr>
<td>divalproex ER</td>
<td>Matrix tablet</td>
<td>Once-daily; only 80% as bioavailable as IR, so dosed 8-20% higher</td>
</tr>
<tr>
<td>galantamine ER</td>
<td>Multiparticulate, reservoir capsule</td>
<td>Once-daily</td>
</tr>
<tr>
<td>guanfacine ER</td>
<td>Matrix tablet</td>
<td>Cannot be substituted on mg per mg basis with IR</td>
</tr>
</tbody>
</table>

*Generic formulations may use different delivery technologies.*

Additional information was taken from drug inserts, company Web sites, and FDA Web site.
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### Oral Modified-Release Psychotropics

<table>
<thead>
<tr>
<th>Formulation*</th>
<th>Delivery</th>
<th>Profile</th>
</tr>
</thead>
<tbody>
<tr>
<td>lithium</td>
<td>Film-coated matrix tablet</td>
<td>May reduce gastric irritation, lower peak plasma levels, lower peak dose side effects</td>
</tr>
<tr>
<td>quetiapine XR</td>
<td>Film-coated matrix tablet</td>
<td>Once-daily</td>
</tr>
<tr>
<td>paliperidone ER</td>
<td>OROS reservoir tablet</td>
<td>Once-daily; there is no IR formulation</td>
</tr>
<tr>
<td>zolpidem CR</td>
<td>Matrix tablet</td>
<td>May be more effective for sleep maintenance than IR formulation</td>
</tr>
</tbody>
</table>

*Generic formulations may use different delivery technologies.

Additional information was taken from drug inserts, company Web sites, and FDA Web site.

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Transdermal Formulations: Patch

- Impermeable covering membrane
- Drug
- Adhesive
- Skin
- Capillary
Transdermal Formulations

Advantages
• Avoids first-pass metabolism (may reduce side effects, increase efficacy)
• Steady plasma concentrations
• Longer duration of action

Disadvantages
• Patches can be large/visible
• Local skin irritation/rash
• Patches may inadvertently come off
• Proper disposal

# Psychotropics With Transdermal Patch Formulations

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>methylphenidate</td>
<td>10 mg/9 hr</td>
</tr>
<tr>
<td></td>
<td>15 mg/9 hr</td>
</tr>
<tr>
<td></td>
<td>20 mg/9 hr</td>
</tr>
<tr>
<td></td>
<td>30 mg/9 hr</td>
</tr>
<tr>
<td>rivastigmine</td>
<td>4.6 mg/24 hr</td>
</tr>
<tr>
<td></td>
<td>9.5 mg/24 hr</td>
</tr>
<tr>
<td>selegiline</td>
<td>6 mg/24 hr</td>
</tr>
<tr>
<td></td>
<td>9 mg/24 hr</td>
</tr>
<tr>
<td></td>
<td>12 mg/24 hr</td>
</tr>
</tbody>
</table>

Long-Acting Injectables

**Advantages**
- Longer duration of action
- Removes bioavailability problems related to absorption and first-pass metabolism
- Maintains stable plasma concentrations
- Decreased risk of overdose (suicidal patients)

**Disadvantages**
- Injection site reaction
- Risk of infection and hematoma
- Administration difficulties (obese or extremely thin)
- Lack of dosing flexibility
- Cost (for some)

Long-Acting Injectable Technologies

• Development of long-acting injectables
  – Protein engineering of native protein
  – Changes in primary structure
  – Formulations that modify circulating half-life
  – Formulation with excipients that delay uptake from injection site (depot formulations)

• Methods
  – Liposomes
  – Microspheres and nanoparticles
  – Polymeric Gels
  – Implants
  – Prodrugs
## Psychotropics With Long-Acting Injectables

<table>
<thead>
<tr>
<th>Drug</th>
<th>Delivery</th>
<th>Duration</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>aripiprazole</td>
<td>Freeze-dried, water-based</td>
<td>4 weeks</td>
<td>In trials</td>
</tr>
<tr>
<td>fluphenazine</td>
<td>Decanoate salt, oil-based</td>
<td>Up to 4 weeks</td>
<td>Available</td>
</tr>
<tr>
<td>haloperidol</td>
<td>Decanoate salt, oil-based</td>
<td>4 weeks</td>
<td>Available</td>
</tr>
<tr>
<td>iloperidone</td>
<td>Biodegradable microspheres, water-based</td>
<td>4 weeks</td>
<td>In trials</td>
</tr>
<tr>
<td>olanzapine</td>
<td>Pamoate salt, water-based</td>
<td>2 weeks 4 weeks</td>
<td>Available</td>
</tr>
<tr>
<td>paliperidone</td>
<td>Palmitate, water-based</td>
<td>4 weeks 12 weeks</td>
<td>Available</td>
</tr>
<tr>
<td>risperidone</td>
<td>Biodegradable microspheres, water-based</td>
<td>2 weeks 4 weeks</td>
<td>In trials</td>
</tr>
</tbody>
</table>

D₂ Receptor Occupancy as a Function of Plasma Olanzapine Concentrations at 4 Weeks After Injection of 300 mg of Depot (N=14)

Mamo et al. 2008.
Mean $D_2$ Receptor Occupancy Over the 6-Month Study Period (N=14)

* Denotes plasma olanzapine concentrations; shows when injections were administered; n. number of PET scans

Mamo et al. 2008.
BPRS Total Mean Change Over Time

Mamo et al. 2008.
Proprietary and Generic Formulations

- Abbreviated protocol process for generics
- Can rely on efficacy and safety data of the original (proprietary) drug
- Required bioequivalence demonstration
- Allowed testing prior to brand patent expiration
- Handling of patent disputes and extensions
What Is A Generic Drug?

“A copy that is the same as a brand-name drug in dosage, safety, strength, how it is taken, quality, performance, and intended use.”

http://www.fda.gov/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/UnderstandingGenericDrugs/default.htm
Proprietary vs Generic Medications: Criteria for Pharmaceutical Equivalence

Pharmaceutical Equivalence

Contain same active ingredient

Have same dosage form, route of administration, and strength/concentration
Pharmaceutical Alternatives

- Contain same therapeutic moiety
- But are different salts, esters, or complexes of that moiety
- Or are different dosage forms or strengths
  - e.g., tablets vs capsules
Proprietary vs Generic Medications: Criteria for Bioequivalence

Bioequivalence

Have comparable bioavailability* when administered in identical doses in an appropriately designed study.

*90% confidence intervals (CI) of the log-transformed ratios of the generic to the proprietary compound for area under the curve (AUC) and concentration peak ($C_{max}$) fall within 80% to 125%.
Bioavailability

The rate and extent to which the active ingredient or active moiety is absorbed from a drug product and becomes available at the site of action.
Proprietary vs Generic Medications: Criteria for Therapeutic Equivalence

**Pharmaceutical Equivalence**
- Contain same active ingredient
- Have same dosage form, route of administration, and strength/concentration

**Bioequivalence**
- Have comparable bioavailability* when administered in identical doses in an appropriately designed study

**Therapeutic Equivalence**

*90% confidence intervals (CI) of the log-transformed ratios of the generic to the proprietary compound for area under the curve (AUC) and concentration peak ($C_{max}$) fall within 80% to 125%.

US FDA. Approved Drug Products With Therapeutic Equivalence Evaluations 2011.
Proprietary vs Generic Medications: Allowed Differences

- Shape
- Scoring configuration
- Packaging
- Excipients
- Expiration time
- Labeling (within certain limits)
- Release mechanisms
Potential Limitations of the Current Requirements

- Studies conducted in healthy volunteers
- Measure parent drug and active metabolites, but not ratio
- Compare single-dose administration rather than therapeutic doses over time
- Dependence on single in vitro dissolution test to predict in vivo dissolution
- No statistical requirement for $T_{\text{max}}$ or shape of plasma concentration-time curve
- Generics are bioequivalent to the proprietary drug, but are not tested against each other

Bioequivalence vs Therapeutic Equivalence

• For most medications, therapeutic equivalence can be assumed based on established bioequivalence

• For others, the allowed difference in extent and rate of absorption may combine with other differentiating factors to cause therapeutic variations
When Formulation May Matter for Proprietary vs Generic Medications

- Narrow therapeutic index
- Nonlinear pharmacokinetics
- Low water solubility
- Modified-release formulation
  - Change in multiphasic release?
  - Dose-dumping risk?
    - Agents with dose-related side effects
Example: Proprietary/Generic Citalopram IR and Proprietary/Alternative Venlafaxine XR

Celexa vs Gen-Citalopram (40 mg x 8 days)

Effexor XR vs Novo-Venlafaxine XR (75 mg x 5 days with washout)

No significant PK differences
No significant clinical differences

Significantly faster/greater release with Novo
Significantly more side effects

Open-label crossover study; N=12 healthy men for each

The Venlafaxine Extended-Release Saga

• Effexor XR capsules: chemical entity patent expired in 2008; XR capsule formulation patent good until 2017

• Osmotica’s ER tablets approved as a new drug (NDA), not a generic therapeutic equivalent

• Sun’s ER tablets ANDA requires bioequivalence to Osmotica’s (the RLD)

<table>
<thead>
<tr>
<th>Effexor XR capsule</th>
<th>Osmotica’s ER tablet</th>
<th>Sun’s ER tablet</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiparticulate, drug diffuses through coating on spheroids</td>
<td>Single-unit, osmotic reservoir system</td>
<td>Single-unit, swellable matrix</td>
</tr>
</tbody>
</table>

Example: The Wellbutrin/Budeprion Controversy

• Jan 1 to June 30 2007: FDA received 85 post-marketing reports concerning adverse events in patients switched from Wellbutrin XL 300 mg to Budeprion XL 300 mg

• In 78 cases, there was a reported loss of antidepressant effect

• In some of those 78 cases and in an additional 7 cases, new onset or worsening of side effects was reported

• More than half of those who switched back to Wellbutrin XL 300 mg reported improvement of depression and/or abatement of side effects

• Given the temporal relationship, patients/physicians attributed these effects to the generic product

http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm153270.htm.
When Formulation May Matter: Bupropion

- We know it matters for bupropion IR vs SR vs XL
- The question is whether there is a meaningful difference between XL proprietary and generic

<table>
<thead>
<tr>
<th>Wellbutrin XL tablet</th>
<th>Budeprion XL tablet</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single-unit, reservoir system, diffusion through coating</td>
<td>Single-unit, matrix system</td>
</tr>
</tbody>
</table>
Wellbutrin XL vs Budeprion XL

Mean Plasma Concentration (ng/mL)

Time (hr)

Clinically relevant?

300 mg strength was not studied due to risk of seizures at higher doses

http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm153270.htm.
When Formulation May Matter: Bupropion

• FDA response: therapeutically equivalent
  – Small PK differences are within equivalence boundaries
  – Earlier $T_{\text{max}}$ with generic is similar to Wellbutrin SR and slower than Wellbutrin IR
  – Recurrent nature of MDD offers a reasonable explanation for the reports of lack of efficacy following switch to generic
  – Asked Teva (mfr) to run head-to-head trial

• Potential dose dumping with generic formulation?

• May consider avoiding generic formulations for
  – Patients who drink alcohol
  – Patients who have the same risk factors for seizure as cited for bupropion IR
Improving FDA Criteria for Bioequivalence: Suggested Additional Measures

- Partial AUC at different times after dosing
- Comparison of shape of concentration-time profiles
- Consideration of subject-by-formulation interaction using replicated or enrichment study designs
- Examination of within-subject variation and lot-to-lot variability
- Clinical equivalence studies using biomarkers or surrogate endpoints
- Use of quality-by-design

Generic Substitutions: Physician and Patient Perceptions

- Aware that pharmacist may substitute without physician consent: 70% Physicians, 60% Patients
- Aware of mandatory generic substitution laws: 40% Physicians, 50% Patients
- Prefer generic if there are potential cost savings: 50% Physicians, 60% Patients
- Concerned about efficacy of generics for acute care
- Concerned about safety of generics for acute care

Questions were focused on anticonvulsants.

State Laws/Statutes Governing Generic Substitution

- Automatic generic substitution by pharmacist unless physician indicates “brand only”
- Legislated “brand only” for anticonvulsants
- Legislated that narrow therapeutic range drugs must be dispensed as prescribed
- Pharmacist’s decision to substitute if “brand only” not indicated by physician

When Formulation May Matter: Prescribing Decisions and Educating Patients

- Patients are less likely to fill prescriptions that are DAW, so make the request discriminately
- Probably not necessary for immediate-release drugs
- For controlled-release drugs, may depend on the release technology used for proprietary vs generic
- Might be most important for
  - Drugs with rapid onset of therapeutic/side effects
  - Drugs with rapid offset of therapeutic/side effects
  - Drugs with dose/plasma level-dependent side effects
  - Drugs with narrow therapeutic index
  - Patients who drink alcohol (important to determine amount/frequency)
- When prescribing DAW, explain to patients why it is important
When Formulation May Matter: Prescribing Decisions and Educating Patients

• When generic alternatives are reasonable
  – Explain this to patient
  – Advise patient to inform you/pharmacist if there is any change in symptoms or side effects following switch to generic
  – Advise patients to note the generic’s distributor and manufacturer and request the same generic each time