INHIBITORS OF NOREPINEPHRINE REUPTAKE

General MC/PC Objective: Understand the role of biogenic amine reuptake pumps: (see CB Notes)

- Why do biogenic amine presynaptic nerves (NE, DA, 5-HT) take up neurotransmitters from the synaptic cleft? **First step in termination** (MAO is in presynaptic nerve)
- How is biogenic amine reuptake accomplished? **By a high affinity, active uptake pump (U-1)**
- How is reuptake coupled to intra-neuronal neurotransmitter metabolism? **See below**
- What other substances may be taken into presynaptic nerves by active reuptake transporters? **Any structural analogue of NE and other neurotransmitters**

Specific MC/PC Objective: Understand the role of NE reuptake pumps: **See below**

![Diagram of adrenergic nerve ending and reuptake process]

- Why do adrenergic nerves take up NE from the synaptic cleft? **Termination**
- How is NE reuptake accomplished? What is the transporter and characterize the nature of the process? **Active U-1 pump**
- How is reuptake coupled to intra-neuronal NE metabolism? **See above**
- What other substances may be taken into presynaptic nerves by active NE reuptake transporters? **NE structural analogues**
- Why do NE reuptake inhibitors have utility in the treatment of depression?
MC Objective: Sub-categorize the drugs capable of inhibiting NE reuptake based on their general structure. Note that most (BUT NOT ALL!) of these compounds are "tricyclics". Since these compounds are used to treat depression, they are commonly referred to as the tricyclic antidepressants (TCADs).

• Dibenzazepine TCADs

\[
\begin{array}{c|c|c}
X & R_1 & R_2 \\
\hline
\text{Imipramine:} & H & \text{CH}_3 \; \text{( tertiary amine)} \\\n\text{Desipramine:} & H & H \; \text{( secondary amine)} \\\n\text{Trimipramine:} & \text{CH}_3 & \text{CH}_3 \; \text{( tertiary amine)} \\\n\text{Clomipramine:} & H & \text{CH}_3 \; \text{( tertiary amine)} \\
\end{array}
\]

• Dibenzocycloheptane-type TCADs

\[
\begin{array}{c|c|c}
X & R_2 \\
\hline
\text{Amitriptyline:} & \text{CH}_3 \; \text{( tertiary amine)} \\\n\text{Nortriptyline:} & H \; \text{( secondary amine)} \\\n\text{Doxepin:} & \text{CH}_3 \; \text{( tertiary amine)} \\
\end{array}
\]

• Dibenzoxazepine TCADs

Amoxepine

• Tetracyclic ADs

Maprotiline

Cyclohexyphenethylamine ADs

Venlafaxine
MC Objective: What role does the tricyclic (other cyclic) ring system play in affinity for NE reuptake transporters (see figure below)?

- Explain why dibenzazepine, dibenzocycloheptane and dibenzoxazepine ring systems have relatively high affinity for NE reuptake transporters?

  - The TC ring systems present in these compounds have the appropriate functionality and three-dimensional structure to interact efficiently with NE and 5-HT reuptake pumps (but not efficiently with DA reuptake pumps!)

- Which other structural feature in the TCADs and related compounds is essential for NE reuptake pump inhibitory activity?

  - The terminal secondary or tertiary amine group is essential for binding to reuptake pumps and determines relative selectively for NE versus 5-HT pumps. Reuptake pump selectivity and adverse reaction profiles are determined primarily by the degree of substitution on the terminal amine groups as described in the sections that follow:

- What is the contribution does the 3 atom bridge between the tricyclic (mulcyclic) ring structure and the terminal amine toward NE reuptake inhibitory activity?

  - The three atom side chain between the tricyclic ring system and terminal amine is an important “spacer” group for the key binding moieties:

MC Objective: Sub-categorize the drugs capable of inhibiting NE reuptake as "secondary amines" or "tertiary amines" based on the degree of "terminal" amine substitution. Describe the impotant of this subclassification in terms of reuptake inhibitory activity.

- TCAD Structure and Reuptake Pump Selectivity: The TCADs are sub-classified structurally as "secondary amines" or "tertiary amines" based on the degree of "terminal" amine substitution as shown in the examples below. Generally, secondary and tertiary amine TCADs have different relative binding affinities for NE and 5-HT reuptake pumps as illustrated by the Table below:

<table>
<thead>
<tr>
<th>Imipramine (Tertiary Amine)</th>
<th>Desipramine (Secondary Amine)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH₃</td>
<td>CH₃</td>
</tr>
<tr>
<td>CH₃</td>
<td>N-CH₃</td>
</tr>
<tr>
<td>N-CH₃</td>
<td>H</td>
</tr>
</tbody>
</table>

![Imipramine and Desipramine structures]
Secondary amine TCADs are relatively potent inhibitors of NE reuptake, and relatively weak inhibitors of 5-HT reuptake. See the example of Desiramine with a very high affinity (low IC\(_{50}\): 0.0056 uM) for NE pumps and much lower affinity for 5-HT pumps (3.4 uM). Also compare amitriptyline to nortriptyline!

Tertiary amine TCADs have lower affinity for NE reuptake pumps than secondary amine TCADS, but higher affinity for 5-HT reuptake pumps than secondary amines. Note the example of Imipramine with an IC\(_{50}\) of 0.81 uM for 5-HT pumps (higher affinity than desipramine for these pumps), and an IC\(_{50}\) of 0.066 uM for NE pumps (lower affinity than desipramine). Also compare amitriptyline to nortriptyline!

Generally secondary amine TCADs have higher selectivity for NE reuptake pumps than 5-HT pumps. This is indicated by their relatively affinities as indicated by the NE/5-HT ratio.

Generally, none of the TCADs have high affinity for dopamine reuptake pumps.

PC/MC Objective: Characterize the general pharmacologic and therapeutic properties of the TCAD-type drugs:

- Characterize the “acute” (immediate) neurochemical actions of TCADs and related compounds (decreased NE biocynthesis and release).

- Characterize the “chronic” actions of the TCAD-type compounds: (downregulation and desensitization of alpha-2 receptors)

- Characterize the neurochemical actions of the TCAD-like compounds at 5-HT neurons?

- What is the primary therapeutic use for the TCADs?

- Why is onset of action of therapeutic action 2-3 weeks?
PC/MC Objective: Characterize the general adverse reaction profile of the TCAD-type drugs:

- In addition to containing the basic pharmacophore to bind to and inhibit NE and 5-HT reuptake pumps, the TCADs also contain the basic pharmacophore capable of binding to and functioning as antagonists at a number of neurotransmitter receptors
  
  - Tertiary amine TCADs have higher affinities for muscarinic receptors and function as antagonists at these receptors. Thus tertiary amine TCADs are more likely to drugs produce anticholinergic side effects in the CNS and PNS. Tolerance does develop to some of these side effects!

  - Tertiary amine TCADs have higher affinities for histamine-1 receptors and function as antagonists at these receptors. Thus tertiary amine TCADs are more likely to drugs produce antihistaminic side effects in the CNS (sedation) and PNS. Tolerance does develop to some of these side effects!

  - Tertiary amine TCADs have higher affinities for alpha-1 receptors and function as antagonists at these receptors. Thus tertiary amine TCADs are more likely to drugs produce alpha-1 antiadrenergic side effects in the CNS and PNS (orthostatic hypotension). Tolerance does develop to some of these side effects!

  - Because of the wide range of neurochemical actions of the tertiary amine TCADs, this subclass of TCADs is more likely to cause sedation, seizures and weight gain. But these are only general adverse reaction trends as illustrated by several examples below!

  - By what biochemical mechanism do the TCAD-type drugs cause adverse reactions such as tachycardia and arrhythmias? Which TCAD-like compound is most likely to induce cardiac arrhythmias? Protriptyline

  - Why should the TCAD-type drugs be used cautiously in patients with CV disease?

  - Which TCAD-like compound is most likely to induce seizures? Maprotiline!
PC/MC Objective: Characterize the general pharmacokinetic properties of the TCAD-type drugs:

- **Absorption**: As relatively lipophilic compounds with adequate solubility in the GI tract, the TCADs are well absorbed from the GI tract by passive mechanisms.

- **Oral Bioavailability**: Relatively low and highly variable from patient to patient. The TCADs can undergo extensive first pass metabolism by a variety of oxidative processes as described below. Different patients may metabolized TCADs at different rates due to variations in metabolic capabilities. Thus there high inter-patient variability in plasma levels of TCAD drugs?

- **Distribution**: The TCADs are highly planar and lipophilic and thus are highly bound to plasma proteins, but still distribute well to a variety of tissues including the CNS.

- **Elimination**: Most TCADs and metabolites (see below) are eliminated renally.

- **Metabolism**: Most of the TCADs undergo extensive metabolism by MFOs. The major pathways of metabolism are shown below. Note that several of these pathways yield active metabolites, and that **OND metabolism converts tertiary amines to secondary which changes reuptake pump specificity**!

![Diagram of TCAD metabolism](image-url)
Based on the metabolic pathways described above and the structure of individual TCAD drugs, the following “metabolic summaries” can be derived (Table):

<table>
<thead>
<tr>
<th>TCAD</th>
<th>Metabolic Pathway</th>
<th>Activity of metabolite</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imipramine (Tertiary)</td>
<td>Terminal amine OND --&gt; Internal amine OND --&gt; Ring hydroxylation --&gt; Benzyllic Oxidation --&gt;</td>
<td>Change uptake pump selectivity (NE&gt;5-HT) Inactive at both NE and 5-HT pumps Decreased Activity relative to parent drug Decreased activity relative to parent drug</td>
</tr>
<tr>
<td>Desipramine (Secondary)</td>
<td>Terminal amine OND --&gt; Internal amine OND --&gt; Ring hydroxylation --&gt; Benzyllic Oxidation --&gt;</td>
<td>Retains activity of parent (NE&gt;5-HT) Inactive at both NE and 5-HT pumps Decreased Activity relative to parent drug Decreased activity relative to parent drug</td>
</tr>
<tr>
<td>Amitriptyline (Tertiary)</td>
<td>Terminal amine OND --&gt; Ring hydroxylation --&gt;</td>
<td>Change uptake pump selectivity (NE&gt;5-HT) Decreased Activity relative to parent drug</td>
</tr>
<tr>
<td>Nortriptyline (Secondary)</td>
<td>Terminal amine OND --&gt; Ring hydroxylation --&gt;</td>
<td>Retains activity of parent (NE&gt;5-HT) Decreased Activity relative to parent drug</td>
</tr>
<tr>
<td>Trimipramine (Tertiary)</td>
<td>Terminal amine OND --&gt; Internal amine OND --&gt; Ring hydroxylation --&gt; Benzyllic Oxidation --&gt;</td>
<td>Change uptake pump selectivity (NE&gt;5-HT) Inactive at both NE and 5-HT pumps Decreased Activity relative to parent drug Decreased activity relative to parent drug</td>
</tr>
<tr>
<td>Clomipramine (Tertiary)</td>
<td>Terminal amine OND --&gt; Internal amine OND --&gt; Ring hydroxylation --&gt; Benzyllic Oxidation --&gt;</td>
<td>Change uptake pump selectivity (NE&gt;5-HT) Inactive at both NE and 5-HT pumps Decreased Activity relative to parent drug Decreased activity relative to parent drug</td>
</tr>
<tr>
<td>Doxepin (Tertiary)</td>
<td>Terminal amine OND --&gt; Ring hydroxylation --&gt;</td>
<td>Change uptake pump selectivity (NE&gt;5-HT) Decreased Activity relative to parent drug</td>
</tr>
<tr>
<td>Amoxepine (Secondary)</td>
<td>Ring hydroxylation --&gt;</td>
<td>Decreased Activity relative to parent drug</td>
</tr>
<tr>
<td>Loxapine (Tertiary)</td>
<td>Terminal amine OND --&gt; Ring hydroxylation --&gt;</td>
<td>More active relative to parent Decreased Activity relative to parent drug</td>
</tr>
</tbody>
</table>

PC/MC Objective: Characterize the general drug interactions of the TCAD-type drugs:

- **Pharmacokinetic Interactions**

  - Competitive plasma protein interactions with other highly bound drugs including phenytoin, phenylbutazone, phenothiazines, aspirin, etc.
  - TCAD metabolism may be inhibited by phenothiazines, methylphenidiate, oral contraceptives, and some SSRIs (fluoxetine, paroxetine).
  - TCAD metabolism induced by classic cytochrome inducers including barbiturates, anticonvulsants, etc.
• **Pharmacologic Interactions**

- TCADs may potentiate the CNS depressant effects of alcohol and sedatives.

- TCADs may block the actions of a variety of sympathomimetics, tyramine, clonidine, guanethidine, etc. by inhibiting the presynaptic uptake of these drugs.

- TCADs may potentiate the actions of MAOIs resulting in enhanced toxicity (block both mechanisms of neurotransmitter termination!)

- TCADs may potentiate the actions of anti-adrenergic drugs (alpha-1), antimuscarinics and antihistaminics (by function as antagonists at these receptors

**General Objective:** Design of selective serotonin reuptake inhibitors (SSRIs):

- NOTE: The adverse reaction and drug interaction profiles of the TCADs and MAOIs stimulated research to find new, safer drugs for the treatment of depression. These efforts led to introduction of the selective serotonin reuptake inhibitors (SSRIs) in the 1980s. These drugs are discussed in more detail in the Serotonin Chapters.

**General Objective:** Design of selective norepinephrine reuptake inhibitors (SNRIs):

- NOTE: The therapeutic limitations of the TCADS and MAOIs (adverse reactions, drug interactions, efficacy) as well as the SSRIs (efficacy, drug interactions, etc) led to the development of selective norepinephrine reuptake inhibitors (SNRIs or NARIs).

**PC/MC Objective:** The first SNRI/NARI available in the US is Reboxetine Mesylate (Vestra®). This drug has been marketed in the UK as Edronax®. Describe the chemical and pharmacological properties of this drug:

![Reboxetine molecule](image)

**Reboxetine**

• What are the general physicochemical properties of reboxetine (acid/base)? **Base**
• Reboxetine contain two chiral centers and is marketed as a racemic mixture of the S,S- and R,R-enantiomers. Are both enantiomers equi-active? **no**
• Is reboxetine relatively selective in its pharmacologic actions? Does it inhibit the reuptake of other neurotransmitters? No. Does it possess clinically significant affinity for 5-HT, DA, NE, mAChR or histamine receptors? Minimal

• Reboxetine is extensively metabolized by CYP 3A4 (and not other major CYPs) enzymes. Which metabolites may form?

• Explain why reboxetine does not induce any CYP isozymes, it can inhibit CYP 3A4 and 2D6 isozymes

• Explain why ketoconazole (Nizoral), erythromycin (E-mycin) and inducers (eg, rifampin [Rifadin], phenytoin [Dilantin]) may affect the metabolism of reboxetine.

• Why is reboxetine less likely than SSRIs to induce “central serotonergic syndrome”?

• Explain why patients with liver disease may clear reboxetine more slowly.

• Why should reboxetine not be used in combination with an MAOI or within 7 days of initiating or 14 days of discontinuing therapy with an MAOI.

General Objective: TCADs, MAIOs, SSRIs and NARIs in therapy:

"An important aim of drug development has been to retain efficacy while reducing side effects and toxicity. It is now clear that selective serotonin reuptake inhibitors (SSRIs) are more effective than noradrenaline reuptake inhibitors (NARIs) in the treatment of obsessional compulsive disorder, and obsessional features in depression predict a responsivity to SSRIs. Furthermore, panic disorder and depression may be more responsive to SSRIs than NARIs. However, there is evidence that inhibition of both sites produces slightly greater efficacy and the addition of an NARI has been reported to potentiate the antidepressant effect of SSRIs. Tricyclic noradrenaline-serotonin uptake inhibitors have many other pharmacological properties, which probably relate to high rates of side effects and cardiotoxicity. Whether in practice these features reduce compliance or increase deaths from suicide is debatable, but it seems wrong to subject patients to burdensome side effects. Certainly, in overdose, older non-selective antidepressants are far more likely to kill than SSRIs. SSRIs have their own side effects, such as nausea and anorgasmia, due to their potency at the uptake site, but these are reversible and sometimes treatable. Clearly, selectivity for specific uptake sites matters for efficacy, and selectivity for uptake over other sites matters for tolerability and safety."

SUMMARY OF THE PHARMACOLOGIC PROFILES OF THE TCADs

Oral Administration

Absorption

GI MEMBRANES

Metabolites (decr activity?) (see notes for structures)
- ONS
- Benzylic oxidation
- Aromatic Hydroxylation
- N-Oxidation

Metabolism

LIVER

Muscarinic receptors

Alpha-1 Receptors

Histamine Receptors

Brain AND Peripheral NS:
“Side Effects”

BLOOD-BRAIN BARRIER

NE and some drugs (ANBs, etc.)

NE

Uptake-1

MAO

10