### Tricyclic Antidepressant Chemistry, Dose, Indication, Receptor Specificity, & Pharmacokinetics

With permission from Kelsie W. Flynn PharmD, PGY-1 Pharmacy Practice Resident. Reviewed and edited by Timothy J Atkinson PharmD

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<table>
<thead>
<tr>
<th>Chemical Structure</th>
<th>Form &amp; Strength Available</th>
<th>FDA Indication</th>
<th>Starting dose</th>
<th>Therapeutic dose for pain</th>
<th>Antidepressant target dose</th>
<th>Receptor Antagonism (Ki)</th>
<th>ADRs</th>
<th>Adverse Drug Reactions</th>
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<tr>
<td>Tertiary Amines</td>
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<tr>
<td>Amtriptyline (Elavil®)</td>
<td>Tablet: 10, 25, 50, 75, 100, 150mg</td>
<td>MDD</td>
<td>10mg, increase by 10mg q3-7d</td>
<td>25-75mg</td>
<td>150-300mg</td>
<td>NA: 50</td>
<td>High risk: Anticholinergic, drowsiness, weight gain and sexual dysfunction Moderate risk: Orthostatic hypotension, QTC prolongation and sexual dysfunction</td>
<td></td>
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<tr>
<td>Imipramine (Tofranil®)</td>
<td>Tablet: 10, 25, 50mg Capsule: 75, 100, 125, 150mg</td>
<td>MDD, Nocturnal Enuresis</td>
<td>10mg, increase by 10mg q3-7d</td>
<td>50-150mg</td>
<td>150-300mg</td>
<td>NA: 60</td>
<td>High risk: Anticholinergic, drowsiness, weight gain and sexual dysfunction Moderate risk: Orthostatic hypotension, QTC prolongation and sexual dysfunction</td>
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</tbody>
</table>
| Doxepin (Silenor®) | Tablet: 3, 6mg Capsule: 10, 25, 50, 75, 100, 150mg | Alcoholism, MDD, GAD, Insomnia, Pruritus | 10mg, increase by 10mg q3-7d | N/A                      | 100-300mg                  | NA: 29.5                 | High risk: Weight gain and drowsiness Moderate risk: Anticholinergic, QTC prolongation, orthostatic hypotension and sexual dysfunction | Moderate risk: Weight gain and drowsiness Moderate risk: QTC prolongation Low risk: Orthostatic hypotension and drowsiness
| Clomipramine (Anafranil®) | Capsule: 25, 50, 75mg | OCD            | 25mg, increase by 25mg q3-7d days | 25-75mg                    | 150-300mg                  | NA: 54                  | High risk: Anticholinergic, drowsiness, weight gain and sexual dysfunction Moderate risk: QTC prolongation Low risk: Orthostatic hypotension and drowsiness | Moderate risk: QTC prolongation Low risk: Ortophastatic hypotension and anticholinergic
| Nortriptyline (Pamelor®) | Tablet: 10, 25, 50, 75, 100, 150mg | MDD            | 10mg, increase by 10mg q3-7d | 50-150mg                  | 150-300mg                  | NA: 10                  | Moderate risk: Sexual dysfunction Moderate risk: QTC prolongation Low risk: Orthostatic hypotension and drowsiness | Moderate risk: Sexual dysfunction Moderate risk: QTC prolongation Low risk: Orthostatic hypotension and anticholinergic
| Desipramine (Norpramin®) | Tablet: 5, 10mg | MDD            | 25mg, increase by 25mg q3-7d | N/A                      | N/A                       | NA: 0.18                 | Moderate risk: Orthostatic hypotension and drowsiness | Moderate risk: Orthostatic hypotension and drowsiness
| Protriptyline (Vivactil®) | Tablet: 25, 50, 100, 150mg | MDD            | 25mg, increase by 25mg q3-7d | N/A                      | N/A                       | NA: 1.41                 | Moderate risk: Drowsiness and QTC prolongation Low risk: Anticholinergic, orthostatic hypotension and weight gain |
| Secondary Amines   |                           |                |               |                           |                           |                         |      |                        |
| Clomipramine (Anafranil®) | Tablet: 10, 25, 50, 75, 100, 150mg | MDD            | 10mg, increase by 10mg q3-7d | 25-75mg                    | 150-300mg                  | NA: 10                  | High risk: Anticholinergic, drowsiness, weight gain and sexual dysfunction Moderate risk: Orthostatic hypotension, QTC prolongation and sexual dysfunction |
| Diphenhydramine (Benadryl®) | Tablet: 5, 10mg | MDD            | 25mg, increase by 25mg q3-7d | N/A                      | N/A                       | NA: 1.41                 | Moderate risk: Drowsiness and QTC prolongation Low risk: Anticholinergic, orthostatic hypotension and weight gain |
| Amoxapine (Asendin®) | Tablet: 25, 50, 100, 150mg | Bipolar, MDD, Dysthymia, Mixed GAD/MDD | 25mg, increase by 25mg q3-7d | N/A                      | 100-225mg                  | NA: 11.1                 | Moderate risk: Drowsiness and QTC prolongation Low risk: Anticholinergic, orthostatic hypotension and weight gain |

Smaller Ki values represent greater potency. *Ki from clinical trials in rats. No human data available.

Receptors--NA: Noradrenergic reuptake, 5-HT: Serotonin reuptake, H1: Histamine 1, Alpha1: Alpha 1 adrenergic, Musc: Muscarinic acetylcholine, 5-HT2a: Serotonin alpha 2

All data was extracted from PDSP Ki database, http://pdsp.med.unc.edu/pdsp.php

Therapeutic doses for pain were pulled from literature which showed efficacy in pain with limited side effect profile

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Bioavailability
- Tertiary Amines: 30-60%
- Secondary Amines: N/A

Protein binding
- Tertiary Amines: 90% or more
- Secondary Amines: 88%

Metabolism
- Major: 2C19 demethylation → nortriptyline (active)
- Minor: 2C9, 1A2 and 3A4 demethylation → nortriptyline (active)
- Minor: 2D6 hydroxylation → 10-hydroxy amitriptyline (inactive)

- Major: 2C19 → desipramine (active)
- Minor: 1A2 and 3A4 → desipramine (active)
- Minor: 2D6 demethylation → 2-hydroxy-imipramine (inactive)

- Major: 2D6 hydroxylation → E-OH-doxepin (inactive)
- Major: 2C19 demethylation → desmethylamitriptyline (active)
- Minor: 3A4, 2C9 and 1A2 → desmethyldoxepin (active)
- Desmethyldoxepin 2D6 hydroxylation → glucuronidated → inactive metabolite
- Minor: oxidation → doxepin N-oxide → glucuronidated → inactive metabolite

- Major: 2C19 demethylation → desmethyldoxepin (active)
- Active metabolites are inactivated by 2D6 hydroxylation

- Major: 2D6 hydroxylation → 10-hydroxy-nortriptyline (inactive)
- Minor: 2D6 hydroxylation and 1A2 demethylation → inactive metabolites
- Minor: 2C9רא demethylation → Desmethyl nortriptyline (inactive)

- Major: 2D6 N-oxidation and hydroxylation → inactive metabolites
- Active metabolites are inactivated by glucuronidation

- Major: 2D6 and 1A2 hydroxylation → 8-OH-amoxapine (active)
- Minor: 2D6 and 1A2 hydroxylation → 7-OH-amoxapine (active)

- Active metabolites are inactivated by hydroxylation

Half-life
- Tertiary Amines: 10-46h
- Secondary Amines: 15-41h

Unique Warnings
- Concern for abnormal sleep-related activities have been documented

- Dose related risk of extrapyramidal symptoms (EPS). Associated with neuroleptic malignant syndrome (NMS); monitor closely.
Common to all TCAs:

- **Seizures**: Potentially lower seizure threshold. Seizures are directly related to dose and serum level and are thus more likely to occur at higher doses and in overdoses.
- **Cardiac**: Potentially cardiotoxic and should be avoided in susceptible individuals with heart disease. In patients with ischemic heart disease, tricyclics can increase cardiac work and decrease heart rate variability, possibly increasing the risk of sudden death. Patients on high doses may also be at increased risk for sudden cardiac death even in the absence of underlying heart disease. TCAs have a higher risk of myocardial infarction compared with SSRIs.
- **Diabetes Mellitus**: Cation in patient with diabetes mellitus as TCAs may alter glucose regulation.
- **Mood**: May precipitate a shift to mania or hypomania in patients with bipolar disorder.
- **Serotonin Syndrome**: Potentially life-threatening serotonin syndrome has occurred with serotonergic agents (e.g. SSRIs, TCAs, SNRIs), particularly when used in combination with other serotonergic agents (e.g., triptans, fentanyl, tramadol, Buspirone, St. John’s Wort).
- **MAOI Interaction**: Co-administration with Monoamine Oxidase Inhibitors (MAOIs) may cause serious side effects and even death has been reported. Do not administer TCA if patient is currently on MAOIs or has used MAOIs within the past two weeks. The exact length of time may vary depending on the particular MAOI dosage and duration of treatment.
- **Glaucoma**: TCAs are contraindicated in individuals with untreated narrow angle glaucoma.
- **Black Box Warning**: Antidepressants increased the risk of suicidal thinking and behavior in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24, and there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. This risk must be balanced with the clinical need. Monitor patients closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Not approved for use in pediatric patients.

References:

5. J. Jornil, K. Linnet Role of polymorphic enzymes CYP2D6 and CYP2C19 for in vitro metabolism of amitriptyline at therapeutic and toxic levels. Forensic Toxicol., 27 (2009), pp. 12–20

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