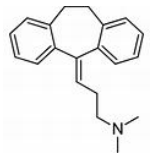
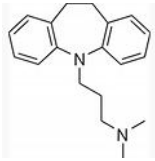
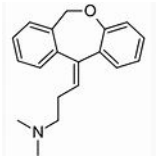
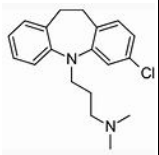
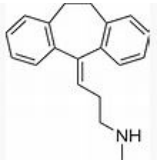
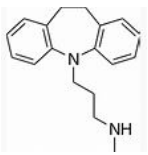
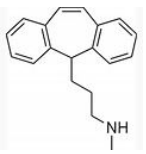
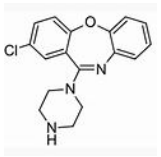
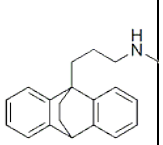
Tricyclic Antidepressant Chemistry, Dose, Indication, Receptor Specificity, & Pharmacokinetics

With permission from Kelsie W. Flynn PharmD, PGY-1 Pharmacy Practice Resident. Reviewed and edited by Timothy J Atkinson PharmD
August 2015

	Tertiary Amines				Secondary Amines				
	Amitriptyline (Elavil®)	Imipramine (Tofranil®)	Doxepin (Silenor®)	Clomipramine (Anafranil®)	Nortriptyline (Pamelor®)	Desipramine (Norpramin®)	Protriptyline (Vivactil®)	Amoxapine (Asendin®)	Maprotiline (Ludiomil®)
Chemical Structure									
Form & Strength Available	Tablet: 10, 25, 50, 75, 100, 150mg	Tablet: 10, 25, 50mg Capsule: 75, 100, 125, 150mg	Tablet: 3, 6mg Capsule: 10, 25, 50, 75, 100, 150mg	Capsule: 25, 50, 75mg	Capsule: 10, 25, 50, 75mg	Tablet: 10, 25, 50, 75, 100, 150mg	Tablet: 5, 10mg	Tablet: 25, 50, 100, 150mg	Tablet: 25, 50, 75mg
FDA Indication	MDD	MDD, Nocturnal Enuresis	Alcoholism, MDD, GAD, Insomnia, Pruritus	OCD	MDD	MDD	MDD	MDD	Bipolar, MDD, Dysthymia, Mixed GAD/MDD
Starting dose	10mg, increase by 10mg q3-7d	10mg, increase by 10mg q3-7d	10mg, increase by 10mg q3-7d	25mg, increase by 25mg q3-7 days	10mg, increase by 10mg q3-7d	25mg, increase by 25mg q3-7d	10mg, increase by 10mg q3-7d	25mg, increase by 25mg q3-7d	25mg, increase by 25mg q3-7d
Therapeutic dose for pain	25-75mg	50-150mg	N/A	50-100mg	25-75mg	50-150mg	N/A	N/A	25-75mg
Antidepressant target dose	150-300mg	150-300mg	150-300mg	100-300mg	50-150mg	150-300mg	15-60mg	200-300mg	100-225mg
Receptor Antagonism (Ki)	NA: 50 5-HT: 20 H1: 1 $Alpha_1$: 27 Musc: 18 $5\text{-}HT_{2a}$: 29	NA: 60 5-HT:7 H1: 40 $Alpha_1$: 32 Musc: 46 $5\text{-}HT_{2a}$: 80	NA: 29.5 5-HT: 68 H1: 0.24 $Alpha_1$: 24 Musc: 83 $5\text{-}HT_{2a}$: 25	NA: 54 5-HT: 0.14 H1: 15 $Alpha_1$: 32 Musc: 25 $5\text{-}HT_{2a}$: 35	NA: 10 5-HT:100 H1: 6.3 $Alpha_1$: 55 Musc: 37 $5\text{-}HT_{2a}$: 44	NA: 0.18 5-HT: 18 H1: 110 $Alpha_1$: 100 Musc: 100 $5\text{-}HT_{2a}$: 280	NA: 1.41 5-HT: 19.6 H1: 60* $Alpha_1$: N/A Musc: N/A $5\text{-}HT_{2a}$: 26*	NA: 16 5-HT: 290 H1: N/A $Alpha_1$: N/A Musc: N/A $5\text{-}HT_{2a}$: 0.5	NA: 11.1 5-HT: 5,800 H1: 1.67 $Alpha_1$: N/A Musc: N/A $5\text{-}HT_{2a}$: 51*
ADRs	High risk: Anticholinergic, drowsiness, weight gain and sexual dysfunction Moderate risk: Orthostatic hypotension, QTc prolongation	High risk: Orthostatic hypotension Moderate risk: Weight gain, anticholinergic, drowsiness, QTc prolongation and sexual dysfunction	High risk: Weight gain and drowsiness Moderate risk: Anticholinergic, QTc prolongation, orthostatic hypotension and sexual dysfunction	Moderate risk: Anticholinergic, drowsiness, weight gain and sexual dysfunction Low risk: Orthostatic hypotension and QTc prolongation	Moderate risk: QTc prolongation Low risk: Anticholinergic and drowsiness	Moderate risk: QTc prolongation Low risk: Orthostatic hypotension and drowsiness	High risk: Sexual dysfunction Moderate risk: QTc prolongation Low risk: Orthostatic hypotension and anticholinergic	Moderate risk: Insomnia and agitation, Low risk: Anticholinergic, drowsiness, orthostatic hypotension, QTc prolongation and weight gain	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, $Alpha_1$: Alpha 1 adrenergic, Musc: Muscarinic acetylcholine, $5\text{-}HT_{2a}$: 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

Compiled by Kelsie W. Flynn PharmD, PGY-1 Pharmacy Practice Resident. Reviewed and edited by Tim Atkinson PharmD

	Tertiary Amines				Secondary Amines				
	Amitriptyline (Elavil®)	Imipramine (Tofranil®)	Doxepin (Silenor®)	Clomipramine (Anafranil®)	Nortriptyline (Pamelor®)	Desipramine (Norpramin®)	Protriptyline (Vivactil®)	Amoxapine (Asendin®)	Maprotiline (Ludiomil®)
Bioavailability	30-60%	30-75%	25%	45-50%	45-85%	40%	75-90%	N/A	88%
Protein binding	90% or more	86%	76-80%	97-98% Desmethylclomipramine is 97-99%	93-95%	73-92%	90% or more	90%	60-90%
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 → desmethyldoxepin (active) **Minor:** 3A4, 2C9 and 1A2 → desmethyldoxepin (active) Desmethyldoxepin 2D6 hydroxlation→ glucuronidated → inactive metabolites **Minor:** oxidation → doxepin N-oxide → glucuronidated → inactive metabolite	**Major**: 2C19 demethylation → desmethylclomipramine (active) **Minor**: 1A2 and 3A4 → desmethylclomipramine (active) Active metabolites are inactivated by 2D6 hydroxylation	**Major:** 2D6 hydroxylation → 10-hydroxy-nortrityline (inactive) **Minor:** 2D6, 1A2 and 2C19 demethylation → Desmethyl nortriptyline (inactive)	**Major:** 2D6 hydroxylation and 1A2 demethylation → inactive metabolites **Minor:** 2C19 demethylation → inactive metabolites	**Major:** 2D6 N-oxidation and hydroxylation → inactive metabolites	**Major:** 2D6 and 1A2 hydroxylation → 8-OH-amoxapine (active) **Minor:** 2D6 and 1A2 hydroxylation → 7-OH-amoxapine (active) Active metabolites are inactivated by glucuronidation	**Major:** 2D6 N-demethylation, →desmethylmaprotiline (active) **Minor:** 1A2 N-demethylation, →desmethylmaprotiline (active) Active metabolites are inactivated by hydroxylation
Half-life	10-46h	8-21h	8-36h	15-37h	13-90h	15-50h	53-92h	15-41h	27-58h
Unique Warnings			Concern for abnormal hazardous sleep-related activities have been documented					Dose related risk of extrapyramidal symptoms (EPS). Associated with neuroleptic malignant syndrome (NMS); monitor closely.	

Compiled by Kelsie W. Flynn PharmD, PGY-1 Pharmacy Practice Resident. Reviewed and edited by Tim Atkinson PharmD

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:

1. Olesen OV, Linnet K. Hydroxylation and demethylation of the tricyclic antidepressant nortriptyline by cDNA-expressed human cytochrome P-450 isozymes. Drug Metab Dispos 1997; 25: 740–744.
2. P. Su, R. T. Coutts, G. B. Baker, and M. Daneshtalab: Analysis of imipramine and three metabolites produced by isozyme CYP2D6 expressed in a human cell line. Xenobiotica 23, 1289–1298 (1993).
3. Koya, Chiba K, Tani M, Ishizaki T: Reappraisal of human CYP isoforms involved in imipramine N-demethylation and 2-hydroxylation: a study using microsomes obtained from putative extensive and poor metabolizers of S-mephenytoin and eleven recombinant human CYPs. J Pharmacol Exp Ther 1997, 281(3):1199-1210.
4. Venkatakrishnan K, Greenblatt DJ, Von Moltke LL, Schmider J, Harmatz JS, Shader RI. Five distinct human cytochromes mediate amitriptyline N-demethylation in vitro: dominance of CYP 2C19 and 3A4. J Clin Pharmacol. 1998;38(2):112–121. doi: 10.1002/j.1552-4604.1998.tb04399.x.
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
6. Gillman P. K. Tricyclic antidepressant pharmacology and therapeutic drug interactions updated. Br. J. Pharmacol. 2007, 151, 737–748.
7. Leijon G, Boivie J. Central post-stroke pain - a controlled trial of amitriptyline and carbamazepine. Pain 1989;36:27–36.
8. Cardenas DD, Warms CA, Turner JA. Marshall. Brooke, Loeser JD. Efficacy of amitriptyline for relief of pain in spinal cord injury:results of a randomized controlled trial. Pain 2002;96:365–73.
9. Kvinesdal B, Molin J, Frøland A, Gram LF. Imipramine treatment of painful diabetic neuropathy. J Am Med Assoc 1984;251:1727–30.
10. Gomez-Perez FJ, Rull JA, Dies H, Rodriguez-Rivera G, Gonzlez-Barranco J, Lozano-Castan˜eda O. Nortriptyline and fluphenazine in the symptomatic treatment of diabetic neuropathy. A double-blind cross-over study. Pain 1985;23:395–400.
11. Max MB, Culnane M, Schafer SC, Gracely RH, Walther DJ, Smoller B, Dubner R. Amitriptyline relieves diabetic neuropathy pain in patients with normal or depressed mood. Neurology 1987;37:589–96.
12. Sindrup SH, Gram LF, Brøsen K, Eshøj O, Mogensen EF. The selective serotonin reuptake inhibitor paroxetine is effective in the treatment of diabetic neuropathy symptoms. Pain 1990a;42:135–44.

Compiled by Kelsie W. Flynn PharmD, PGY-1 Pharmacy Practice Resident. Reviewed and edited by Tim Atkinson PharmD

13. Sindrup SH, Gram LF, Skjold T, Grodum E, Brøsen K, Beck-Nielsen H.Clomipramine vs desipramine vs placebo in the treatment of diabetic neuropathy symptoms. A double-blind cross-over study. Br J Clin Pharmacol 1990b;30:683–91.
14. Max MB, Schafer SC, Culnane M, Smoller B, Dubner R, Gracely RH. Amitriptyline, but not lorazepam, relieves postherpetic neuralgia. Neurology 1988;38:1427–32.
15. Max MB, Kishore-Kumar R, Schafer SC, Meister B, Gracely R, Smoller B, Dubner R. Efficacy of desipramine in painful diabetic neuropathy: a placebo-controlled trial. Pain 1991;45:3–9.
16. Max MB, Lynch SA, Muir J, Shoaf SE, Smoller B, Dubner R. Effects of desipramine, amitriptyline, and fluoxetine on pain in diabetic neuropathy. N Engl J Med 1992;326:1250–6.
17. Vrethem M, Boivie J, Arnqvist H, Holmgren H, Lindstro¨m T, Thorell L-H. A comparison of amitriptyline and maprotiline in the treatment of painful polyneuropathy in diabetics and nondiabetics. Clin J Pain 1997;13:313–23.
18. Sindrup SH, Bach FW, Madsen C, Gram LF, Jensen TS. Venlafaxine versus imipramine in painful polyneuropathy. A randomized, controlled trial. Neurology 2003;60:1284–9.
19. Sindrup SH, Jensen TS. Pharmacological treatment of pain in polyneuropathy.Neurology 2000;55:915–20.
20. Rowbotham MC, Goli V, Kunz NR, Lei D. Venlafaxine extended release in the treatment of painful diabetic polyneuropathy: a double-blind, place controlled study. Pain 2004;110:697–706.
21. Watson CP, Evans RJ, Reed K, Merskey H, Goldsmith L, Warsh J. Amitriptyline versus placebo in postherpetic neuralgia. Neurology 1982;32:671–3.
22. Kishore-Kumar R, Max MB, Schafer SC, Gaughan AM, Smoller B, Gracely RH, Dubner R. Desipramine relieves postherpetic neuralgia. Neurology 1990;47:305–12.
23. Raja SN, Haythornthwaite JA, Pappagallo M, Clark MR, Travison TG, Sabeen S, Royall RM, Max MB. Opioids versus antidepressants in postherpetic neuralgia. A randomized, placebo-controlled trial. Neurology 2002;59:1015–21.
24. Robinson LR, Czerniecki JM, Ehde DM, Edwards WT, Judish DA, Goldberg ML, Campbell KM, Smith DG, Jensen MP. Trial of amitriptyline for relief of pain in amputees: results of a randomized controlled study. Arch Phys Med Rehab 2004;85:1–6.
25. Kieburtz K, Simpson D, Yiannoutsos C, Max MB, Hall CD, Ellis RJ, Marra CM, McKendall R, Singer E. Dal Pan GJ. Clifford DB, Tucker T, Cohen B and the AIDS Clinical Trial Group 242 Protocol Team. A randomized trial of amitriptyline and mexiletine for painful neuropathy in HIV infection. Neurology 1998;51:1682–8.
26. Kalso E, Tasmuth T, Neuvonen PJ. Amitriptyline effectively relieves neuropathic pain following treatment of breast cancer. Pain 1995;64:293–302.
27. Panerai AE, Monza G, Movilia P, Bianchi M, Francucci BM, Tiengo M. A randomized, within-patient, cross-over, placebo-controlled trial on the efficacy and tolerability of the tricyclic antidepressants chlorimipramine and nortriptyline in central pain. Acta Neurol Scand 1990;82:34–8.
28. Shlay JC, Chaloner K, Max MB, Flaws B, Reichelderfer P, Wentworth D, Hillman S, Brizz B, Cohn DL. the Terry Beirn Community Programs for Clinical Research on AIDS. Acupuncture and amitriptyline for pain due to HIV-related peripheral neuropathy. JAMA 1998;280:1590–5.
29. Tasmuth T, Ha¨rtel B, Kalso E. Venlafaxine in neuropathic pain following treatment of breast cancer. Eur J Pain 2002;6:17–24.
30. Verdu B., Decosterd I., Buclin T., et al: Antidepressants for the treatment of chronic pain. Drugs 2008; 68: pp. 2611-2632
31. Moore R.A., Derry S., Aldington D., et al: Amitriptyline for neuropathic pain and fibromyalgia in adults (review). Cochrane Database Syst Rev 2012; undefined:
32. McCleane G.: Antidepressants as analgesics. CNS Drugs 2008; 22: pp. 139-156
33. O'Malley P.G., Balden E., Tomkins G., et al: Treatment of fibromyalgia with antidepressants: a meta-analysis. J Gen Intern Med 2000; 15: pp. 659-666
34. Kroenke K., Krebs E.E., and Bair M.J.: Pharmacotherapy of chronic pain: a synthesis of recommendations from systematic reviews. Gen Hosp Psychiatry 2009; 31: pp. 206-219
35. Klit H, Finnerup NB, Jensen TS. Central post-stroke pain: clinical characteristics, pathophysiology, and management. Lancet Neurol 2009; 9: 857–868. (class I SR).
36. Siddall PJ, Cousins MJ, Otte A, Griesing T, Chambers R, Murphy TK. Pregabalin in central neuropathic pain associated with spinal cord injury: a placebo-controlled trial. Neurology 2006; 67: 1792–1800. (class I).
37. Hempenstall K, Nurmikko TJ, Johnson RW, A_Hern RP, Rice AS. Analgesic therapy in postherpetic neuralgia: a quantitative systematic review. PLOS medicine 2005; 2:e164. class I SR).
38. Rowbotham MC,Attal N, Cruccu G, Haanpa¨ a¨ M, et al. EFNS Task Force. EFNS guidelines on pharmacological treatment of neuropathic pain. Eur J Neurol 2006; 13: 1153–1169. (class I SR).
39. Saarto T, Wiffen PJ. Antidepressants for neuropathic pain. Cochrane Database Syst Rev. 2007, 4: CD005454.(class I SR).
40. Finnerup NB, Otto M, McQuay HJ, Jensen TS, Sindrup SH. Algorithm for neuropathic pain treatment: an evidence based proposal. Pain 2005; 118: 289–305. (class I SR).
41. Kadiroglu AK, Sit D, Kayabasi H, Tuzcu AK, Tasdemir N, Yilmaz ME. The effect of venlafaxine HCl on painful peripheral diabetic neuropathy in patients with type 2 diabetes mellitus. J Diabetes Complications 2008; 22: 241–245. (class II).
42. Baumann,P.:Pharmacogenetics of antidepressant metabolism. Value of the debrisoquine test. Encephale 1986, 12, 143-148.
43. Brachtendorf L, et al. Cytochrome P-450 enzymes contributing to demethlation of maprotiline in man. Pharmacology & Toxicaology, 2002, 90,:3 144-149
44. Serretti A, Chiesa A. Sexual side effects of pharmacological treatment of psychiatric disease. Clin Pharm Ther 2011; 89:142.
45. Wenzel-Seifert K, Wittmann M, Haen E: QTc prolongation by psychotropic drugs and the risk of torsade de pointes. Dtsch Arztebl Int 2011; 108;687.