

Utah Medicaid Pharmacy & Therapeutics

Drug Class Review

Antidepressant, Tricyclic (TCAs)

Antidepressants 28:16.04.28

Amitriptyline (Elavil®, generic)

Amitriptyline and Chlordiazepoxide (Limbitrol®, others, Limbitrol DS®)

Amitriptyline and Perphenazine (generic)

Amoxapine (generic)

Clomipramine (Anafranil®, generic)

Desipramine (Norpramin®, generic)

Doxepin (Prudoxin®, Silenor®, Zonalon®, generic)

Imipramine (Tofranil®, imipramine HCl, imipramine pamoate)

Maprotiline (generic)

Nortriptyline (Pamelor®, generic)

Protriptyline (Vivactil®, generic)

Trimipramine (Surmontil®, generic)

Final Report
September, 2016

Review Prepared by:

Vicki Frydrych, BS, PharmD, Clinical Pharmacist

Joanne LaFleur, PharmD, MSPH, Associate Professor

Carin Steinvoort, PharmD, Clinical Pharmacist

University of Utah College of Pharmacy

Copyright © 2016 by University of Utah College of Pharmacy

Salt Lake City, UT. All rights reserved

Contents

Executive Summary	3
Introduction.....	5
Table 1: Comparison of TCA Antidepressants.....	6
Table 2: Comparison of FDA Approved and Labeled Indications	14
Disease Overview:	15
Major Depressive Disorder	15
Table 3. Current Clinical Practice Guidelines for the Treatment of Depressive Disorders.....	17
Generalized Anxiety Disorder (GAD)	21
Table 4: Current Clinical Practice Guideline for Drug Treatment of Anxiety Disorders.....	23
Obsessive-Compulsive Disorder.....	25
Table 5: Current Clinical Practice Guidelines for the Treatment of Obsessive-Compulsive Disorder.....	26
Post-Traumatic Stress Disorder (PTSD).....	30
Table 6: Current Clinical Practice Guidelines for Treatment of PTSD	31
Insomnia.....	32
Table 7: Current Clinical Practice Guidelines for the Treatment of Insomnia	33
Bipolar Disorder Disease Overview	35
Table 8. Current Clinical Practice Guidelines for the Treatment of Bipolar Disorder	37
Schizophrenia.....	39
Table 9. Current Clinical Practice Guidelines for the Treatment of Schizophrenia	42
Diabetic Neuropathy	44
Table 10: Current Clinical Practice Guideline for the Treatment of Diabetic Peripheral Neuropathy.....	45
Pharmacology	47
Table 11: Pharmacokinetics of TCAs.....	48
Special Populations	50
Table 12: Special Populations.....	51
Methods.....	53
Clinical Evidence	53
Safety	59
Table 13: Pharmacologic Activity and Adverse Event Profile of TCAs	61
Table 14: Drug Interactions with TCA Antidepressants.....	63
Summary:.....	65
References.....	69

Executive Summary

Introduction:

This review includes the tricyclic antidepressants (amitriptyline, clomipramine, desipramine, doxepin, imipramine, nortriptyline, protriptyline, trimipramine), tetracyclic antidepressants (amoxapine, maprotiline) and two amitriptyline combination products (amitriptyline-chlordiazepoxide, amitriptyline-perphenazine). Each of the tricyclic/tetracyclic antidepressants (TCAs) is available in an oral tablet or capsule formulation. Doxepin is additionally available in a topical formulation and both doxepin and nortriptyline are available as oral solutions.

Although first developed for their anticholinergic and sedative side effects, antidepressant activity was discovered and these agents found their major use in mental illness. Of the single-entity agents, each is labeled for the treatment of depression except clomipramine, which is labeled only for use in obsessive-compulsive disorder. Doxepin is additionally labeled for use in anxiety-depressive disorders, insomnia and pruritus. Maprotiline carries labeling for use in anxiety depressive disorders, bipolar-depressed phase disorder and dysthymia. Imipramine is labeled for use in nocturnal enuresis. The combination products, amitriptyline-perphenazine and amitriptyline-chlordiazepoxide, are both labeled for anxiety depressive disorders with amitriptyline-perphenazine also labeled for use in schizophrenia and depression.

Clinical Efficacy:

Evidence supporting the use of tricyclic antidepressants is limited with issues of bias, power, robustness and significant heterogeneity in both measuring instruments and populations. Additionally, methodological and reporting shortcomings are common. For instance, trials of migraine prophylaxis were of too short duration. Overall, data was not assessed to the level of the individual medication. The majority of evidence is categorized as low to very low quality according to Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) guidelines and further studies are needed to confirm the place of TCAs in therapy. Pooled together, the evidence suggests the following:

Depression: Efficacy of TCAs was not different than fluoxetine in the treatment of major depressive disorder, although fluoxetine was better tolerated than amitriptyline, clomipramine and imipramine. Pooled TCAs (desipramine, imipramine and nortriptyline) appear to perform as well as SSRIs in the physically-ill depressed, with an earlier response to treatment. Amitriptyline performed statistically, but not clinically, superior to grouped comparators (SSRIs, tricyclic and tetracyclic antidepressants) in the treatment of depression, although amitriptyline therapy was associated with more adverse events and lower tolerability. Pooled TCAs (amitriptyline, clomipramine, desipramine, dothiepin, doxepin, imipramine, nortriptyline) were as efficacious as SSRIs and atypical antidepressants and in treating the depressed elderly. TCAs may be more efficacious in preventing recurrence during depression-maintenance-therapy in the elderly. Low-dose TCA therapy (<100 mg daily of amitriptyline, clomipramine, desipramine, doxepin and trimipramine) was as effective as standard dose therapy for the treatment of depression and associated with fewer adverse events. Evidence does not support the use of TCAs in the treatment of depressed adults with cancer or in the treatment of children or adolescents with depression or anxiety disorders.

Pain: Amitriptyline use in fibromyalgia pain is supported with weak evidence. In the treatment of non-cancer/non-HIV neuropathic pain, low to very-low quality evidence supports amitriptyline, clomipramine, desipramine and nortriptyline as equally efficacious. Evidence does not support the use of amitriptyline, imipramine, desipramine, trimipramine or dothiepin for use in

rheumatoid arthritis pain. Additionally, the use of TCA therapy was ineffective to improve depressive symptoms in depressed rheumatoid arthritis patients with pain.

Irritable Bowel Syndrome: Evidence found the TCAs efficacious in reducing irritable bowel syndrome symptom score and abdominal pain, but individual TCA comparative evidence is lacking.

ADHD: In the treatment of ADHD, desipramine and nortriptyline demonstrated improvement in core symptoms but was not found superior to methylphenidate. Cardiovascular side effects should limit the utility of TCAs in children, pending the availability of further evidence.

Insufficient Evidence: Evidence is limited and insufficient to support a role for desipramine or imipramine in the treatment of nocturnal enuresis; for amitriptyline or desipramine in treatment of tension headache; for amitriptyline in migraine prophylaxis or for clomipramine in autism spectrum disorder.

Safety:

Many of the adverse effects of TCA therapy relate to pharmacological activity. TCAs may cause confusion, delirium, delayed cardiac conduction, orthostatic hypotension, seizures, photosensitivity and the precipitation of glaucoma. A narrow therapeutic range can produce cardiotoxicity and seizures at doses less than 10 times the daily recommended dose, with children at higher risk than adults. TCAs should be used cautiously in the elderly who are more sensitive to TCA anticholinergic side effects and orthostatic hypotension. TCAs should be avoided or used with caution in patients with underlying cardiovascular disease or conduction defects. MAOIs may increase the risk of suicidality in young people and may activate mania/hypomania in patients with undiagnosed bipolar disorder. TCAs, especially clomipramine, may worsen psychosis, delusions and agitation in psychiatric patients. TCAs increase insulin sensitivity in diabetes and may increase bone fracture risk. TCAs may cause bone marrow suppression, sexual dysfunction, weight gain and abrupt discontinuation may cause a withdrawal reaction. Hepatotoxicity may occur with clomipramine. Amoxapine use is associated with neuroleptic malignant syndrome and tardive dyskinesia. TCAs, particularly amitriptyline, may increase the risk of venous thromboembolism.

Some of the most common mechanisms by which tricyclic antidepressants produce drug interactions include additive effects with other serotonergic medications, CYP450 enzyme interactions and anticholinergic mediated cardiac and cardiovascular effects. Potentially fatal serotonin syndrome may occur with TCAs in combination with MAOIs or serotonin reuptake inhibitors including SSRIs, SNRIs as well as with the weak serotonin inhibitors, meperidine, fentanyl and tramadol. TCAs should not be used within 14 days of discontinuing MAOI therapy. TCAs interact with hepatic microsomal metabolism of other medications and substrates, although the effect is less significant than with SSRIs/SNRIs.

Summary:

The TCAs are effective antidepressants but are not first-line therapy for the treatment of depression as safer alternatives are available. Good quality comparative evidence is lacking and evidence does not identify any TCA superior to another in studies of good quality for any indication. Selection of TCA therapy should consider patient comorbidities, concomitant and recently discontinued medications, use of- and response to prior therapies, the adverse effect/drug interaction/pharmacologic activity profile of the particular TCA and patient and prescriber preferences.

Introduction

Tricyclic drugs were first investigated for their anticholinergic and sedative properties.¹ When these agents were found to be useful in the treatment of psychiatric illnesses, these same properties became the troublesome side effects.¹ These agents are categorized by their chemical structure. The first-generation compounds are tertiary amine tricyclic agents (amitriptyline, clomipramine, doxepin, imipramine and trimipramine).¹⁻³ The secondary amine tricyclic (desipramine, nortriptyline, protriptyline) and tetracyclic amine compounds (amoxapine, maprotiline) were developed to minimize the side effects associated with the first-generation, tertiary amine agents.¹ Included in this review are the tricyclic antidepressant agents, amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, maprotiline, nortriptyline, protriptyline, trimipramine and the combination agents amitriptyline/chlordiazepoxide and amitriptyline/perphenazine.

Each of the tricyclic antidepressants is available in oral tablet or capsule formulations. Additionally, doxepin is available in a topical formulation and both doxepin and nortriptyline are available as oral solutions. Of the single-entity agents, each is labeled for the treatment of depression, except clomipramine which is labeled only for use in obsessive-compulsive disorder. Doxepin is additionally labeled for use in anxiety-depressive disorders, insomnia and pruritus. Maprotiline is additionally labeled for use in anxiety depressive disorders, bipolar-depressed phase disorder and dysthymia. Imipramine is additionally labeled for use in nocturnal enuresis. The combination products are both labeled for anxiety depressive disorders, while amitriptyline-perphenazine is additionally labeled for use in schizophrenia and depression. See **Table 1** for a comparison of the agents and **Table 2** for FDA approved and labeled indications.⁴⁻⁶

Table 1: Comparison of TCA Antidepressants

	Available Formulations	Indications/Uses	Oral Dose Range, Adults	Oral Dose Range, Pediatrics	Generic
Amitriptyline	<p>Oral Tablet: 10 mg, 25 mg, 50 mg, 75 mg, 100 mg, 150 mg</p> <p>Elavil Oral Tablet: 25 mg</p>	<p>Depression</p> <p><u>Unlabeled Use:</u> Fibromyalgia, Headache,</p> <p>Irritable bowel syndrome (treatment and prophylaxis), Pain,</p> <p>Polyneuropathy</p>	<p><u>Depression</u></p> <p>Initial: 75 mg in 1 to 3 doses daily up to a MAX of 150 mg daily. Inpatients may start with 100 mg and increase to 300 mg.</p> <p>Maintenance: 50 to 100 mg at bedtime</p> <p><u>Polyneuropathy</u></p> <p>Initial: 10 to 25 mg daily at bedtime. May increase weekly to a MAX dose 150 to 200 mg daily.</p> <p><u>Subjective tinnitus</u></p> <p>Initial: 50 mg at bedtime x 7 days then increase to 100 mg at bedtime.</p>	<p>Not established in children < 12 years</p> <p><u>Depression</u></p> <p>Initial: 10 mg three times daily and 20 mg at bedtime.</p>	Yes
Amoxapine	<p>Oral Tablet: 25 mg, 50 mg, 100 mg, 150 mg</p>	<p>Depression</p> <p><u>Unlabeled Use</u> Endogenous depression</p> <p>Severe major depression with psychotic features</p>	<p><u>Depression</u></p> <p>Initial: 50 mg 2 to 3 times daily. May increase dose by 100 mg up to 2-3 times daily</p> <p>OR</p> <p>300 mg daily with first few days of sedation notable. May increase to 400 mg after 3 weeks of suboptimal response (no convulsive disorder). Hospitalized patients, cautiously up to 600 mg daily</p> <p>Maintenance: 120-300 mg daily</p> <p><u>Endogenous depression</u></p> <p>Initial: 50 mg 2 to 3 times daily. May increase up to 100 mg 2 to 3 times a day at one week</p> <p>OR start with 300 mg daily with first few days of notable sedation.</p>	<p>Not established in children < 16 years</p>	Yes

	Available Formulations	Indications/Uses	Oral Dose Range, Adults	Oral Dose Range, Pediatrics	Generic
			<p>Maintenance: Usual effective dose is 120-300 mg daily. May increase to 400 mg daily after 3 weeks of inadequate response. Hospitalized patients without seizures may be increased cautiously to 600 mg daily.</p> <p><u>Severe major depression with psychotic features</u></p> <p>Initial: 50 mg 2 to 3 times daily. May increase up to 100 mg 2-3 times a day after 7 days</p> <p>OR 300 mg daily with several days of notable sedation.</p> <p>Maintenance: Usual effective dose is 120-300 mg daily. May increase dosage to 400 mg daily after 3 weeks of inadequate response. Hospitalized patients with no history of convulsive seizures may be increased cautiously to 600 mg daily</p>		
Clomipramine (Anafranil®)	<p>Oral Capsule: 25 mg, 50 mg, 75 mg</p> <p>Anafranil Oral Capsule: 25 mg, 50 mg, 75 mg</p>	<p>Obsessive-Compulsive Disorder</p> <p><u>Unlabeled Use</u></p> <p>Delusional disorder</p> <p>Depression</p> <p>Disorder of ejaculation</p> <p>Obsessive-compulsive disorder</p>	<p><u>Delusional disorder</u></p> <p>Initial: 25 mg daily. May increase to 100 mg daily during the first 2 weeks. Mean effective dose, 140 mg daily.</p> <p>MAX: 250 mg daily</p> <p><u>Depression</u></p> <p>Initial: 75 mg daily in 3 divided doses. May increase slowly to a 100-250 mg daily.</p> <p><u>Obsessive-compulsive disorder</u></p> <p>Initial: 25 mg daily. May increase to 100 mg daily over the first 2 weeks.</p>	<p>Safety and effectiveness in children < 10 years of age not established</p> <p><u>Depression</u></p> <p>Initial: 20-30 mg daily. May increase by 10 mg daily every 4-5 days as needed and tolerated.</p> <p><u>Obsessive-compulsive disorder</u></p> <p>Age ≥ 10 years</p>	Yes

	Available Formulations	Indications/Uses	Oral Dose Range, Adults	Oral Dose Range, Pediatrics	Generic
		Intravenous therapy Chronic pain	MAX: 250 mg daily <u>Panic disorder</u> 25-75 mg/day	Initial: 25 mg daily. May increase to the lesser or 3 mg/kg or 100 mg/day over the first 2 weeks. MAX: 200 mg daily or 3 mg/kg/day (the lesser)	
Desipramine (Norpramin®)	Oral Tablet: 10 mg, 25 mg, 50 mg, 75 mg, 100 mg, 150 mg Norpramin Oral Tablet: 10 mg, 25 mg, 50 mg, 75 mg, 100 mg, 150 mg	Depression <u>Unlabeled Use</u> Attention deficit hyperactivity disorder (ADHD) Diabetic neuropathy	<u>Depression</u> Initial: 100-200 mg daily in single or divided doses. MAX: 300 mg daily <u>Diabetic neuropathy</u> Initial: 100-200 mg daily as single or divided doses	Not established <u>Attention deficit hyperactivity disorder</u> Initial: 25 mg daily. May increase to MAX 5 mg/kg/day divided doses as needed and tolerated <u>Depression</u> Adolescents: 25-100mg daily in single or divided doses to MAX 150 mg daily.	Yes
Doxepin	Oral Capsule: 10 mg, 25 mg, 50 mg, 75 mg, 100 mg, 150 mg Oral Tablet: 3 mg, 6 mg Oral Solution: 10 mg/1 ML Topical Cream: Prudoxin 5%, Silenor 5%, Zonalon	Alcoholism/Anxiety with Depression, Anxiety/Depression, Anxiety/Depression with Psychoneurotic personality disorder, Insomnia,	<u>Alcoholism - Anxiety - Depression</u> <u>Very mild</u> , Initial: 25 to 50 mg daily gradually increase to MAX 300 mg daily if needed. <u>Mild to moderate</u> , Initial: 75 mg daily in single or divided doses, increase to usual range 75 to 150 mg daily or MAX dose 300 mg daily as needed (divided doses) <u>Anxiety - Depression</u> <u>Very mild</u> , initial: 25 to 50 mg daily and increase as needed to MAX 300 mg daily.	Not established <u>Alcoholism - Anxiety - Depression</u> <u>Age > 12 years</u> <u>Very mild</u> , initial: 25 to 50 mg daily, increase gradually as needed MAX 300 mg daily <u>Age > 12 years</u> <u>Mild to moderate</u> , initial: 75 mg daily in single or	Yes (oral) No (Topical)

	Available Formulations	Indications/Uses	Oral Dose Range, Adults	Oral Dose Range, Pediatrics	Generic
		<p>Pruritus (moderate) due to atopic dermatitis or lichen simplex chronicus</p> <p><u>Unlabeled Use</u> Urticaria</p>	<p><u>Mild to moderate</u>, initial: 75 mg daily in single or divided doses, increase to usual dose 75 to 150 mg daily or as needed to MAX 300 mg daily</p> <p><u>Anxiety - Depression - Psychoneurotic personality disorder</u></p> <p><u>Outpatients</u>: 75 mg daily in 1 to 3 divided doses. MAX 150 mg daily</p> <p><u>Inpatients</u>: 150 mg daily in 1 to 3 divided doses. MAX 300 mg daily</p> <p><u>Insomnia</u></p> <p>Age < 65 years: 6 mg daily within 30 minutes of bedtime.</p> <p>Age ≥ 65 years: Initial dose 3 mg daily, may increase to 6 mg daily within 30 minutes of bedtime.</p> <p><u>Pruritus (Moderate), Due to atopic dermatitis or lichen simplex chronicus</u></p> <p>Initial: 10 mg at bedtime, may gradually increase to 25 mg at bedtime</p> <p>Topical: Apply a thin film to skin 4 times a day (3-4 hr between applications) for a MAX of 8 days</p>	<p>divided doses, gradually increase as needed to usual range 75 -150 mg daily</p> <p>MAX 300mg daily</p> <p><u>Anxiety - Depression</u></p> <p>Age ≥ 12 years</p> <p>Very mild, initial: 25-50 mg daily, gradually increase as needed to MAX 300 mg daily</p> <p>Age > 12 years</p> <p>Mild to moderate, 75 mg daily in single or divided doses, increase to usual range 75 to 150 mg daily, as needed to MAX 300 mg daily</p>	
Imipramine (Tofranil, Tofranil PM®)	<p>Oral Tablet: 10 mg, 25 mg, 50 mg</p> <p>Tofranil Oral Tablet: 10 mg, 25 mg, 50 mg</p> <p>Pamoate: Oral Capsule: 75 mg,</p>	<p>Depression</p> <p>Nocturnal enuresis</p> <p><u>Unlabeled Use</u></p> <p>Binging</p>	<p><u>Depression</u></p> <p><u>Inpatients</u>: 100 mg daily in divided doses. May increase to a MAX of 300 mg daily.</p> <p><u>Outpatients</u>: 75 mg daily, may increase to MAX 200 mg daily.</p> <p>Maintenance Dose: 50-150 mg daily.</p>	<p>Not established except for nocturnal enuresis in children ≥ 6 years.</p> <p>Nocturnal enuresis</p> <p><u>Age 6-12 years</u>: Initial, 25 mg 1 hr before bedtime. May increase in 25 mg</p>	Yes

	Available Formulations	Indications/Uses	Oral Dose Range, Adults	Oral Dose Range, Pediatrics	Generic
	100 mg, 125 mg, 150 mg	Diabetic neuropathy Panic disorder Urinary incontinence PAMOATE Depression <u>Unlabeled Use</u> Diabetic neuropathy Panic disorder	<u>Panic disorder</u> Initial: 100-200 mg daily in 1-3 divided doses. Higher doses required with agoraphobia. <u>Urinary incontinence</u> Initial: 25 mg at bedtime. May increase by 25 mg increments to MAX dose of 150 mg at bedtime PAMOATE <u>Depression</u> <u>Inpatients:</u> Initial, 100 to 150 mg at bedtime. Usual maintenance dose 75-150 mg at bedtime. MAX: 300 mg at bedtime. <u>Outpatients:</u> 75 mg at bedtime. Usual maintenance dose 75-150 mg at bedtime. MAX: 200 mg at bedtime. <u>Panic disorder</u> Initial: 100-200 mg daily in 1-3 divided doses. Higher doses required with agoraphobia.	increments to MAX dose 50 mg daily or 2.5 mg/kg/day <u>Age > 12 years:</u> Initial: 25 mg 1 hr before bedtime. May increase in 25 mg increments to 75 mg daily or 2.5 mg/k/day PAMOATE Not established	
Maprotiline	Oral Tablet: 25 mg, 50 mg, 75 mg	Bipolar disorder, depressed phase Depression Dysthymia Mixed anxiety and depressive disorder <u>Unlabeled Use</u> Pain	<u>Bipolar disorder, depressed phase</u> <u>Inpatients:</u> Initial 100-150 mg daily in 2-3 divided doses for 14 days. May increase in 25 mg increments to usual maintenance dose 75-150mg daily. MAX of 225 mg daily in single or divided doses <u>Outpatients:</u> 75 mg daily in 2-3 divided doses for 14 days. May increase in 25 mg increments to MAX 225 mg daily <u>Depression</u>	Not established	Yes

	Available Formulations	Indications/Uses	Oral Dose Range, Adults	Oral Dose Range, Pediatrics	Generic
			<p>Inpatients: 100-150 mg daily in 2-3 divided doses for 14 days. May increase in increments of 25 mg to usual maintenance dose 75-150 mg</p> <p>MAX 225 mg daily in single or divided doses.</p> <p><u>Outpatients:</u> 75 mg daily in 2-3 divided doses for 14 days. May increase increments of 25 mg to MAX 225 mg daily.</p> <p><u>Dysthymia</u></p> <p>Inpatients: 100-150 mg daily for 14 days. May increase in increments of 25 mg to usual maintenance dose of 75-150 mg daily in 2-3 divided doses.</p> <p>MAX: 225 mg daily in single or divided doses</p> <p><u>Outpatients:</u> 75 mg daily in 2-3 divided doses for 14 days. May increase in increments of 25 mg. MAX 225 mg daily</p> <p><u>Mixed anxiety and depressive disorder</u></p> <p><u>Inpatients:</u> 100-150 mg daily in 2-3 divided doses for 14 days. May increase in increments of 25 mg to maintenance 75-150 mg daily. MAX 225 mg daily</p> <p><u>Outpatients:</u> 75 mg daily in 2-3 divided doses for 14 days. May increase in increments of 25 mg</p> <p>MAX: 225 mg daily</p>		
Nortriptyline (Pamelor®)	Oral Capsule: 10 mg, 25 mg, 50 mg, 75 mg	Depression	<p><u>Depression</u></p> <p>Initial: 25 mg in single or divided doses MAX: 150 mg daily</p> <p><u>Smoking cessation assistance</u></p>	<p><u>Depression</u></p> <p>Adolescents: 30 to 50 mg daily in single or divided doses</p>	Yes

	Available Formulations	Indications/Uses	Oral Dose Range, Adults	Oral Dose Range, Pediatrics	Generic
	Oral Solution: 10 mg/5 ML Pamelor Oral Capsule: 10 mg, 25 mg, 50 mg, 75 mg		Begin 1 week prior to smoking cessation date with 75-100 mg daily (may titrate to antidepressant serum levels) for 6-14 weeks.		
Protriptyline (Vivactil®)	Oral Tablet: 5 mg, 10 mg	Depression	<u>Depression</u> Initial: 15 to 40 mg daily in divided doses. May increase morning doses to MAX 60 mg daily in divided doses.	Not established Depression 5 mg ORALLY 3 times a day; may increase gradually if necessary	Yes
Trimipramine (Surmontil®)	Oral Capsule: 25 mg, 50 mg, 100 mg Surmontil Oral Capsule: 25 mg, 50 mg, 100 mg	Depression	<u>Depression</u> <u>Inpatients:</u> 100 mg daily in 1-3 divided doses. Gradually increase over a few days to 200 mg daily in divided doses. After 2-3 weeks with suboptimal response may increase to MAX 250-300 mg daily. <u>Outpatients:</u> 75 mg daily in 1-3 divided doses. Gradually increase over a few days to 150 mg daily in divided doses. Maintenance: 50-150 mg daily at bedtime continued for 3 months. MAX: 200 mg daily	Not established <u>Depression</u> Adolescents: 50 mg daily gradually increased to 100 mg and continued for 3 months.	
Combination Products					
Amitriptyline and Chlordiazepoxide	Oral Tablet: 12.5 mg/5 mg, 25 mg/10 mg	Mixed anxiety and depressive disorder	<u>Mixed anxiety and depressive disorder</u> Range from 12.5 mg/5 mg 3-4 times daily to 25 mg/10 mg up to 6 times daily.	Not established	

	Available Formulations	Indications/Uses	Oral Dose Range, Adults	Oral Dose Range, Pediatrics	Generic
Perphenazine and Amitriptyline	Oral Tablets: 2 mg/10 mg 2 mg/25 mg 4 mg/10 mg 4 mg/25 mg 4 mg/50 mg	Mixed anxiety and depressive disorder Schizophrenia and depression	<u>Mixed anxiety and depressive disorder</u> Initial: 2-4 mg perphenazine/25 mg amitriptyline 3-4 times daily or one 4 mg/50 mg tablet twice daily. Maintenance: 2-4 mg perphenazine/25 mg amitriptyline 2-4 times daily or 4 mg/50 mg twice daily. <u>Severely ill patients with schizophrenia:</u> 8 mg perphenazine /50 mg amitriptyline 3-4 times daily MAX: 16 mg perphenazine/200 mg amitriptyline	Not established in children Adolescents Initial: 4 mg perphenazine/10 mg amitriptyline 3-4 times daily and adjusted as needed	

Table 2: Comparison of FDA Approved and Labeled Indications

	Depression	Obsessive-Compulsive Disorder	Anxiety-Depressive Disorders	Insomnia	Pruritus	Bipolar Depressed Phase	Dysthymia	Schizophrenia and Depression	Nocturnal Enuresis
Amitriptyline	X								
Amoxapine	X		X						
Clomipramine		X							
Desipramine	X								
Doxepin	X		X	X	X				
Imipramine	X								X
Maprotiline	X		X			X	X		
Nortriptyline	X								
Protriptyline	X								
Trimipramine	X								
Combination Products									
Amitriptyline and Chlordiazepoxide			X						
Perphenazine and Amitriptyline			X					X	

Disease Overview:

Major Depressive Disorder

The mood disorders (including major depressive disorder, bipolar I disorder, bipolar II disorder, cyclothymic, persistent depressive disorder (dysthymia) and premenstrual dysphoric disorder) affect approximately one in ten adult Americans.⁷ Major depressive disorder is the most common of the mood disorders, affecting nearly 15% of US adults.⁸ In 2004, depression was listed as the third most common cause of disease burden across the world.⁹ In general, depression occurs more frequently in women than men, in people 40-50 years of age and in patients living below the poverty level. Depressive disorder is linked to increased rates of chronic disease, health care utilization and impaired activities of daily living. Almost half of all patients with depression experience disabilities to maintain healthy work, home and social habits. The economic burden of depression in the US (~\$83.1 billion in 2000) results from increased rates of indirect costs (unemployment, lost productivity, etc.) in addition to direct healthcare costs.¹⁰⁻¹² Depression is frequently underdiagnosed and, even more frequently, depression is inadequately treated. Improving disease education and increasing access to care will help to improve clinical outcomes and save costs.¹³

A Behavioral Health Barometer for Utah by the Substance Abuse and Mental Health Services Administration (SAMHSA) reveals that compared to the US as a whole, youth age 12-17 as well as adults in Utah were more likely to have a major depressive episode.¹⁴ For youth, the rate of a major depressive disorder in Utah compared to the US during 2011/2012 was 10.2% vs 8.7% and in 2012/2013 it was 11.5% vs 9.9%. For adults over the same time periods the rates were 5.1% vs 4% and 5.4% vs 4.1%, respectively.¹⁴

Depression is a serious mental disorder characterized by changes in cognitive and physical behaviors with a loss of pleasure in enjoyable activities.¹³ Major depression is defined as the presence of at least 5 symptoms during a period of at least 2-weeks that reflect a change in previous functioning and causes distress or impairment in normal activities. Symptoms associated with a depressive episode must include sadness and/or loss of interest or pleasure. Other symptoms may include significant unexplained weight loss, insomnia or hypersomnia, agitation, fatigue, feelings of worthless, excessive guilt, reduced ability to concentrate and recurrent thoughts of death. In <2% of the general population depression is not clearly associated with acute distress, impairment or change from previous functioning. The diagnosis of dysthymic disorder includes a persistent depressive mood with chronic (≥ 2 years), ongoing symptoms that tend to be less severe and/or numerous.¹³ Depression with atypical symptoms is a depressive subtype associated with mood reactivity. The diagnosis is made when at least two of the following symptoms are present, significant weight gain or increase in appetite, hypersomnia, leaden paralysis, or a long-standing pattern of interpersonal rejection sensitivity without meeting criteria for melancholic or catatonic features.¹⁵

Drug therapy is the foundation of the medical management of the mood disorders. Before the introduction of the second-generation antidepressants, drug therapy was limited to tricyclic antidepressants and monoamine oxidase inhibitors, known collectively as the first-generation antidepressants. The first generation antidepressants are associated with many intolerable adverse effects (sedation and anticholinergic effects) and are no longer agents of choice for treating most depressive disorders. As a result, the second-generation antidepressants, including

the selective serotonergic agents and serotonin modulators, have become one of the most commonly prescribed drug classes in the US pharmaceutical market, accounting for \$10.9 billion in US prescription sales in 2003.¹⁶ Clinical evidence suggests the most efficacious treatment for depression includes a combination of psychological therapy and medication therapy for at least 6-8 weeks.¹⁷ The goal in treating depression is to reduce the risk of disease/symptom recurrence.¹⁰ There is little evidence to demonstrate one agent or class of antidepressants is more effective than others. A response rate of 70% may be achieved with 6-8 weeks of most any pharmacotherapy. Titration schedules should be conservative, with modest increases from the initial dose each 3 weeks to allow for a clinical response. Aggressively increasing doses may reduce tolerability and increase adverse events. Patience is the key to successful outcomes because it may take 12 weeks for substantial benefit.¹⁸ Treatment is generally continued for 6 to 12 months after stabilization.¹⁸ Almost half of all patients being treated for depression by their primary care provider will discontinue their medication therapy within a month, unless proper education and a treatment plan is provided.¹⁹ Selection of an antidepressant agent should be based on treatment history, comorbid conditions anticipated side effects, clinical evidence and patient preference.^{13,20} In patients demonstrating suicidal ideation, the drug selected should have low toxicity if taken in overdose.^{10,13,20}

Clinical guidelines for the treatment of depression include the World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for Biological Treatment of Unipolar Depressive Disorders Part 1(2013)²¹ and Part 2 (2015)²², the National Institute for Health and Clinical Excellence (NICE) Depression in adults: recognition and management (2009)²³, National Collaborating Center for Health, Mental: The Treatment and Management of Depression in Adults (2010)²⁴, the American Psychiatric Association Practice Guideline for the Treatment of Patients with Major Depressive Disorder (2010)²⁵, Institute for Clinical Systems Improvement (ICSI): Adult Depression in Primary Care (2016)²⁶, Canadian Network for Mood and Anxiety Treatments (CANMAT) Clinical Guidelines for the Management of Major Depressive Disorder in Adults (2016)²⁷ and the American Academy of Child and Adolescent Psychiatry (AACAP): Practice Parameter for the Assessment and Treatment of Children and Adolescents with Depressive Disorders (2007).²⁸ See **Table 3** for a summary of the most current guideline recommendations.

The choice of an initial antidepressant should consider the severity of symptoms, comorbid conditions, psychosocial stressors, biological, psychological, environmental factors, safety, tolerability, anticipated side effects, pharmacologic medication properties (cytochrome P450 (CYP) hepatic enzyme interactions, half-life, drug interactions), cost, patient preference, prior treatment experiences and family history of response. Patients should be advised that a response to therapy may be delayed 4-6 weeks.^{13,29} First-line agents include a second-generation antidepressant (e.g. SSRI, SNRI, mirtazapine, bupropion) for the treatment of depression. If only a partial response is achieved at 4-6 weeks, the dose may be increased (if tolerated) for another 4 weeks. Partial responders may receive an alternative antidepressant, a combination of antidepressant agents or adjunctive treatment with another class of medications including lithium, thyroid hormone, atypical antipsychotic agent or dopamine agonists. A large randomized controlled trial examining Sequenced Treatment Alternatives to Relieve Depression (STAR*D) reported no differences in efficacy between the adjunctive medication classes.³⁰ Medication therapy should be adjusted until a full remission is achieved. Non-responders should be referred to a mental health specialist. MAOIs are restricted to refractory treatment. Treatment should

continue for an additional 6-9 months to prevent relapse. Chronic maintenance therapy is recommended in patients with two or more depression episodes. Cognitive Behavioral Therapy (CBT) is recommended for all patients with depressive disorders.¹³

Table 3. Current Clinical Practice Guidelines for the Treatment of Depressive Disorders

Guideline	Recommendations
<p>World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for biological treatment of unipolar depressive disorder Part 1: (2009)²¹</p>	<p>Medication therapy in combination with psychological counseling is recommended</p> <p>A treatment plan and disease/medication education are recommended for all patients</p> <p>First-line: Antidepressants</p> <p style="padding-left: 40px;">No single class of antidepressants has proven to be more effective than another</p> <p style="padding-left: 80px;">Amitriptyline, clomipramine and venlafaxine have demonstrated increased efficacy in severely depressed hospitalized patients</p> <p>Newer agents (bupropion, trazodone, SSRI, SNRIs, mirtazapine) are generally better tolerated than the older agents</p> <p>In treatment-resistant patients: Consider increasing the dose, switching to another antidepressant agent, combining two antidepressants, augmenting the antidepressant with another agent (best evidence for aripiprazole, lithium, quetiapine)</p>
<p>World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for biological treatment of unipolar depressive disorders. Part 2: Maintenance Treatment of Major Depressive Disorder (Updated 2015)²²</p>	<p><u>Adults:</u> Continue the antidepressant which induced remission or lithium if augmentation was successful. If this fails, consider the combination of antidepressant/lithium. Continue the medication at the same treatment dose</p> <p>Effective agents include</p> <ul style="list-style-type: none"> • Tricyclic antidepressants (TACAs), monoamine oxidase inhibitors (MAOIs), selective serotonin reuptake inhibitors (SSRIs) and selective serotonin norepinephrine reuptake inhibitors (SNRIs). <ul style="list-style-type: none"> ○ Newer antidepressants have better long-term efficacy due to better tolerability and better safety profile compared with older agents (TCAs) • Some data supports quetiapine in maintenance therapy • Evidence is lacking for carbamazepine or other mood stabilizers. <p>Duration of maintenance therapy</p> <ul style="list-style-type: none"> • Discontinuation should always be gradual over at least 3 months. • Acute depressive episode: 6-9 months • Recurrent depressive episode in the prior 5 years or difficult to achieve remission: 3 years • Those at greatest risk: Having a new episode of depression within 1 year after 2 or 3 attempts to discontinue therapy. <p><u>Children and Adolescents</u></p>

Guideline	Recommendations
	<p>SSRIs and SNRIs have limited evidence the continued medication is better than placebo in preventing new episodes with differences in suicidality between groups</p> <p><u>Older Adults</u> Evidence supports use compared with placebo for nortriptyline (tachycardia and dry mouth more common), phenelzine, paroxetine, escitalopram, citalopram but NOT sertraline.</p>
<p>National Institute for Health and Clinical Excellence (NICE) Depression in adults: recognition and management (2009)²³</p>	<p>Mild-Moderate Disorder <u>First-line:</u> low-intensity psychosocial intervention Second-line: antidepressant therapy (typically SSRI) OR a high-intensity psychosocial intervention</p> <p>Moderate-Severe Disorder <u>First-line:</u> combination antidepressant therapy and a high-intensity psychological intervention</p> <p>Antidepressant agents</p> <ul style="list-style-type: none"> • SSRIs have a favorable risk-benefit ratio • Fluoxetine, fluvoxamine and paroxetine are associated with increased risk of drug interactions • Venlafaxine and tricyclic antidepressants are associated with increased risk of death from overdose • Monoamine oxidase inhibitors (MAOIs) should only be prescribed by specialists • In treatment-resistant patients, increase dose or switch to another antidepressant
<p>National Collaborating Centre for Mental Health (UK): Depression British Psychological Society; National Institute for Health and Clinical Excellence: 2010²⁴</p>	<p>Step 1: All known and suspected presentations of depression</p> <ul style="list-style-type: none"> • Assessment, support, psychoeducation, active monitoring and referral for further assessment and interventions <p>Step 2: Persistent subthreshold depressive symptoms; mild to moderate depression</p> <ul style="list-style-type: none"> • Low-intensity psychosocial interventions, psychological interventions, medication and referral for further assessment and interventions • Depression with anxiety: Treat depression first • Anxiety disorder with comorbid depression: Treat anxiety first • Sleep hygiene, active monitoring, low-intensity psychosocial interventions, group cognitive behavioral therapy • Do not use antidepressants routinely with subthreshold depressive or mild depression because the risk-benefit is poor. • Drug therapy is appropriate: Past history of moderate severe depression or subthreshold depression for at least 2 years or symptoms which persist after other interventions • Do not use St John's wort.

Guideline	Recommendations
	<p>Step 3: Persistent subthreshold depressive symptoms or mild to moderate depression with inadequate response to initial interventions; moderate and severe depression</p> <ul style="list-style-type: none"> • High-intensity psychological interventions, combined treatments, collaborative care and referral for further assessment and interventions (Counseling and psychodynamic psychotherapy alone is of uncertain effectiveness) • Medications: SSRI +/- psychological intervention • SSRIs are preferred due to a favorable risk-benefit ratio <ul style="list-style-type: none"> ○ SSRIs increase the risk of bleeding (geriatric, drug-interaction) ○ Fluoxetine, fluvoxamine, paroxetine higher drug-drug interaction potential ○ Paroxetine has more discontinuation symptoms than other SSRIs • Consider toxicity in overdose (TCAs carry the highest risk) • MAOIs should only be prescribed by a specialist • Doxepin should NOT be prescribed • Consider adherence relative to side effects <ul style="list-style-type: none"> ○ Venlafaxine exacerbates cardiac arrhythmias ○ Hypertension exacerbated with venlafaxine/duloxetine ○ TCA induced postural hypotension and cardiac arrhythmias • Lack of response at 3-4 weeks: Increase the medication dose or switch • No evidence suggests treating depression different by subtype, gender, sex or ethnicity • Switching antidepressants: No evidence suggests a difference with between or within classes. Try newer antidepressant SSRI/SNRI again then consider a different less-well tolerated class. <ul style="list-style-type: none"> ○ Consider: fluoxetine long half-life; fluoxetine/paroxetine increase TCA levels, from one serotonergic agent to another due to serotonin syndrome, waiting 2 weeks for non-reversible MAOI washout before starting new agent. • Augmentation: Lithium, antipsychotic, mirtazapine. Do NOT augment with benzodiazepine, buspirone, carbamazepine, lamotrigine or valproate, thyroid hormones or pindolol. <p>Step 4: Severe and complex depression; risk to life; severe self-neglect</p> <ul style="list-style-type: none"> • Medication, high-intensity psychological interventions, electroconvulsive therapy, crisis service, combine treatments, multi-professional and inpatient care • Depression with psychotic symptoms: Augment with antipsychotic (dose and duration unknown)
American Psychiatric Association: Practice Guideline for the Treatment	Acute phase

Guideline	Recommendations
<p>of Patients With Major Depressive Disorder (2010)²⁵</p>	<p>First-line: antidepressant medication (SSRI, SNRI, bupropion, mirtazapine)</p> <ul style="list-style-type: none"> • The effectiveness of antidepressant medications is comparable and initial selection is based on adverse effect profile, prior treatments, cost and patient preference <ul style="list-style-type: none"> ○ If side effects occur, lower dose or switch agents ○ If no response or partial response: increase dose, switch agents or augmenting the antidepressant with another antidepressant or a non-antidepressant medication (lithium, thyroid hormone or a second generation antipsychotic) <p>Continuation phase</p> <ul style="list-style-type: none"> • Continue successful treatment for 6-9 months and monitor for signs of relapse <p>Maintenance phase</p> <ul style="list-style-type: none"> • Continue successful treatment in patients with three or more depressive episodes or with additional risk factors for relapse <p>Discontinuation of treatment</p> <ul style="list-style-type: none"> • Taper the medication over the course of at least several weeks <p>Other notes</p> <ul style="list-style-type: none"> • Combination of antipsychotic and antidepressant medications is recommended in patients with psychotic symptoms
<p>Institute for Clinical Systems Improvement (ICSI): Major Depression in Adults in Primary Care (2016)²⁶</p>	<p>Recommended pharmacotherapy:</p> <ul style="list-style-type: none"> • SSRIs, venlafaxine, duloxetine, desvenlafaxine, mirtazapine, bupropion <p>Other options:</p> <ul style="list-style-type: none"> • Secondary amine tricyclics (TCAs), monoamine oxidase inhibitors (MAOIs) <p>Augmentation therapy:</p> <ul style="list-style-type: none"> • Bupropion, buspirone, mirtazapine, triiodothyronine (T3), stimulants, TCA-SSRI combination, lithium, atypical antipsychotics <p>Recommended in patients with treatment-resistant or partially-responsive disease: Referral to a mental health specialist</p>
<p>Canadian Network for Mood and Anxiety Treatments (CANMAT) Clinical guidelines for the management of major depressive disorder in adults (2016)²⁷</p>	<p>Selection</p> <ul style="list-style-type: none"> • Based on disease severity, comorbid conditions, adverse effect profile, treatment history, potential drug–drug interactions, patient preference and cost; Use of antidepressant should be accompanied by patient education, close monitoring (1-4 weeks) and self-management techniques

Guideline	Recommendations
	<p>First-line recommendations</p> <ul style="list-style-type: none"> Bupropion, citalopram, desvenlafaxine, duloxetine, escitalopram, fluoxetine, fluvoxamine, milnacipran, mirtazapine, paroxetine, sertraline, venlafaxine <p>Second-line recommendations</p> <ul style="list-style-type: none"> Amitriptyline, clomipramine and other tricyclic antidepressant (TCA) agents; quetiapine; selegiline; trazodone <p>Third-line recommendations</p> <ul style="list-style-type: none"> Phenelzine, tranylcypromine
<p>American Academy of Child and Adolescent Psychiatry (AACAP): Practice Parameter for the Assessment and Treatment of Children and Adolescents with Depressive Disorders (2007)²⁸</p>	<p>A confidential relationship should be maintained with the child or adolescent</p> <p>Psychiatric assessments should routinely be made</p> <p>Treatment should always include an acute and continuation phase, some may require maintenance treatment</p> <p><u>First-line:</u> Supportive psychotherapy</p> <p><u>Second-line:</u> Psychotherapy and/or antidepressants</p> <ul style="list-style-type: none"> Selective serotonin reuptake inhibitors (SSRIs) are the most commonly used pharmacotherapy in pediatric patients Clinical response should be assessed at 4-week intervals <ul style="list-style-type: none"> If inadequate response, increase dose Treatment should be continued for 6-12 months Atypical antipsychotics, combined with SSRIs, are recommended as the treatment of choice for depressed psychotic pediatric patients

Generalized Anxiety Disorder (GAD)

Generalized anxiety disorder (GAD) manifests with worry that is persistent, excessive and often unrealistic.^{2,31} Physical complaints commonly include muscle tension, an inability to concentrate and arousal symptoms (e.g. restlessness and insomnia). The diagnosis of GAD is made when excessive worry and anxiety are difficult to control, with symptoms on more than half the days over 6 months in association with a number of psychological and/or physical findings.³² Diagnosis is most commonly made before age 20 in people who grew up with childhood fears. It is believed there is a genetic component, as the illness is common in those who have first-degree relatives with the illness. Psychiatric comorbidities are common, including major depression, dysthymia or social phobia. Patients often self-medicate with alcohol or sedative/hypnotics.³³⁻³⁶

Treatment involves a combination of psychotherapy and pharmacotherapy and is often initiated with a short course of a benzodiazepine.^{31,32,34-38} Lorazepam,

oxazepam and alprazolam are preferred agents due to low hepatic metabolism and a lack of active metabolites. Medications are initiated at the lowest dose and used only as-needed. The more rapidly absorbed agents have the most rapid onset of action but also the greatest abuse/dependence potential. Longer acting agents may accumulate resulting in sedation, cognitive impairment and psychomotor retardation. Short acting agents may produce anxiety, insomnia and more rebound effects upon discontinuation. Safe discontinuation of any benzodiazepines is by a slow taper. Transitioning patients from long-acting to short-acting agents may allow more flexibility and aid in discontinuing therapy. Adjunctive carbamazepine or beta-blockers may be useful in the discontinuation process. Buspirone is anxiolytic, which may be effective in the treatment of generalized anxiety disorders but requires multiple daily doses and several weeks before a response is seen. The SSRI agents escitalopram, paroxetine, venlafaxine and duloxetine (a dual-acting antidepressant) are labeled for use in GAD at typical antidepressant doses and may be safer for long-term treatment of chronic anxiety. Other agents which may be effective include doxepin and the GABAergic acting anticonvulsants, divalproex, gabapentin, oxcarbazepine, pregabalin and tiagabine.

Panic Disorder

Panic disorders are unpredictable episodes of fear associated with a sense of impending doom and physical manifestations (e.g. palpitations, sweating, shortness of breath, chest pain, dizziness).^{2,13,31,32,34-36,38,39} Symptoms heighten over 10 minutes and subside within an hour. A diagnosis of a panic disorder requires a one-month history of changes in behavior, worry or concern due to the panic attack. The disorder usually manifests in late adolescence. The goal of therapy is to reduce the number, duration and intensity of attacks. Psychotherapeutic interventions should be initiated upon diagnosis. In 75% of people, treatment reduces but does not eradicate symptoms. Treatment with an SSRI is associated with fewer side effects than with TCAs. Therapy with SSRIs is initiated at low doses, typically 1/3 to 1/2 the antidepressant dose. Patients with atypical depression may benefit from treatment with a MAOI. A clinical response may be delayed up to 6-weeks. Antidepressant doses should be titrated upward as required. Often patients are given short courses of anxiolytics (benzodiazepines) to reduce symptoms until the antidepressant medication becomes effective.

Social Anxiety Disorder (SAD)

SAD reflects a persistent fear of other people in settings in which one's behavior or performance may be judged; or in the presence of strangers.^{2,13,31,32,34-36,38,39} The person remains anxious and unable to function although they realize their fear is irrational. SAD produces an anxiety reaction that may result in panic attacks and may lead to avoidance behaviors impacting social and occupational functioning. Females are more commonly affected. Symptoms often date to early childhood with a diagnosis established by early adulthood. First-line treatment involves cognitive behavior therapy (CBT). Patients unwilling to participate in CBT may be started on SSRIs. Psychodynamic therapy may be useful in patients who decline CBT or drug therapy. Combination CBT/pharmacotherapy is recommended in patients who do not respond to their initial therapy. The use of SNRIs or MAOIs may be tried after first-line therapies fail or produce only a partial response.

Clinical guidelines for the treatment of anxiety disorders include two National Institute for Health and Care Excellence (NICE) guidelines; one addressing the management of generalized anxiety and panic disorders in adults³⁸ and a second developed by the National Collaborating Centre for Mental Health on behalf of NICE addressing social anxiety disorder.³² **Table 4** presents the clinical practice guidelines.

Table 4: Current Clinical Practice Guideline for Drug Treatment of Anxiety Disorders

Guideline	Recommendations
<p>NICE: Generalized anxiety disorder and panic disorder in adults: management. [CG113]³⁸</p>	<p>Step 1: Identify and assess, educate about generalized anxiety disorder (GAD) and treatment options; active monitoring</p> <p>Step 2: Psychological interventions, self-help, individual guided self-help, psychoeducational groups</p> <p>Step 3: Choice of high-intensity psychological intervention (cognitive behavior therapy (CBT) or applied relaxation or drug treatment</p> <p>Psychological Intervention: 12 to 15 1-hour sessions of psychological intervention</p> <p>Pharmacological Treatment:</p> <p><u>First-line:</u> SSRI: Most cost effective; obtain informed consent; monitor adverse effects and response</p> <ul style="list-style-type: none"> • If ineffective, a trial of a second SSRI or an SNRI, considering: <ul style="list-style-type: none"> ○ Withdrawal syndrome with paroxetine, venlafaxine ○ Side-effect and drug interaction profile ○ Risk of suicide, toxicity in overdose (venlafaxine) ○ Prior treatment history (adherence, side effects, withdrawal syndrome, patient preference) • If unable to tolerate SSRI/SNRI, consider pregabalin • No NOT use benzodiazepine except short-term in primary or secondary care • Do NOT use antipsychotics for GAD in primary care • Prior to therapy discuss with the patient – benefits of treatment, drug propensities for side effects, withdrawal reactions, drug interactions, risk of activation symptoms, full anxiolytic effect requiring 1 week or more, importance of adherence/compliance • Consider bleeding risk with SSRIs especially in older people, those taking agents that can damage the gastrointestinal mucosa or interfere with clotting: Consider prescribing a gastroprotective agent • Patients under 30 years: Warn concerning the increased risk of suicidal thoughts and self-harm AND see them in 1 week AND monitor for the first month. • Side effects: Developing soon after initiation of treatment <ul style="list-style-type: none"> ○ Monitor closely for mild symptoms, reduce the dose or stop the drug and initiate an alternative medication or initiate high-intensity psychological intervention • Review effectiveness, side effects every 2-4 weeks for 3 months then every 3 months. • If effective, continue therapy at least one year (relapse rate

Guideline	Recommendations
<p>NICE: Social anxiety disorder: recognition, assessment and treatment NICE guidelines [CG159], 2013³²</p>	<p>is high)</p> <p>IF Step 3 is inadequate: Offer alternative treatment (psychological or pharmaceutical); offer intensive psychological intervention for partial-medication responders or refer to Step 4 if risk of self-harm, suicide, significant comorbidity or self-neglect or inadequate response to Step 3 options.</p> <p>Step 4: Complex drug and/or psychological treatment regimens; input from multi-agency teams, crisis services, day hospitals, inpatient care.</p> <ul style="list-style-type: none"> • Specialist assessment, review patient, family, carers needs, develop a comprehensive care plan. • Treatment: Offer interventions they have not tried <ul style="list-style-type: none"> ○ Consider combining psychological and drug treatments ○ Combinations of antidepressants ○ Augmentation of antidepressants <ul style="list-style-type: none"> ▪ Caution that effectiveness of combination treatments is lacking ▪ Side effects, drug interactions are more likely <p>Interventions for Adults</p> <ul style="list-style-type: none"> • CBT, not group therapy or CBT-based supported self-help. Promote CBT before pharmacological therapy • IF the person wished pharmacologic therapy offer SSRI such as escitalopram or sertraline. Monitor for adverse reactions • IF patients decline both CBT and drug therapy consider psychodynamic therapy <p>For Partial Response to CBT</p> <ul style="list-style-type: none"> • Consider combination of drug therapy and CBT <p>For Partial Response to Drug Therapy (after 12 weeks) or Side Effects</p> <ul style="list-style-type: none"> • Alternative SSRI (fluvoxamine or paroxetine) or SNRI, such as venlafaxine, considering: <ul style="list-style-type: none"> ○ Paroxetine and venlafaxine produce a discontinuation syndrome (extended with ER preparations), risk of suicide and toxicity in overdose <p>For non-response to SSRI/SNRI</p> <ul style="list-style-type: none"> • Consider MAOIs such as phenelzine or moclobemide • Discuss individual CBT <p>Interventions for Children and Young People</p> <ul style="list-style-type: none"> • Individual or group CBT (may involve parents or carers) • NOT recommended <ul style="list-style-type: none"> ○ Pharmacological interventions, including anticonvulsants, tricyclic antidepressants, benzodiazepines, or antipsychotic medication, St. John's wort or other over-the-counter preparations, botulinum toxin for hyperhidrosis

Obsessive-Compulsive Disorder

Obsessive Compulsive Disorder (OCD) is a common, chronic, anxiety disorder characterized by excessive, unrealistic worry about everyday events or tasks which can interfere with all aspects of life. Obsessions are persistent, unwanted, involuntary, intrusive, abnormal thoughts, ideas, urges or images. Compulsions are repeated, ritualized behaviors, undertaken in an attempt to reduce or prevent the anxiety or distress that an obsessive thought precipitates.^{8,33,40-42} Most people are diagnosed with obsessive-compulsive disorder by age 19, although 25% exhibit symptoms as early as age 14.^{33,42} Males present at an earlier age, in greater proportion and often with more severe disease, however, gender distribution in adults is equal or slightly favors females.^{8,43} The Substance Abuse and Mental Health Services Administration (SAMHSA) estimates the 12-month prevalence of OCD in US adults at 1.2%, or affecting 2.2 million people.⁴⁰ Up to fifty percent of cases are classified as severe.³³ The lifetime morbidity risk is 2.7%.⁴⁴ Often OCD occurs with anxiety, depression or body dysmorphic disorder.⁴² Risk factors for the development of OCD, include genetics (first-degree relative), frontal cortex and subcortical brain structure abnormalities, prior exposure to trauma and post-Streptococcal infection (Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections (PANDAS)).⁴⁵

Treatment modalities include psychotherapy, medications or a combination of both.^{37,42,44-46} The most effective medications are SSRIs, SRIs (e.g. clomipramine) and tricyclic antidepressants.^{41,44,47} The doses of antidepressants used for treating OCD are frequently higher than those used for the treatment of depression and the clinical response may be delayed 8-12 weeks.^{41,44,47} Antipsychotic medications are appropriate options for patients unresponsive to other therapies. Cognitive behavior therapy (CBT) or habit reversal training were shown as effective as medication therapy, while Exposure and Response Prevention (ERP) demonstrated efficacy in patients failing serotonergic medications.⁴² Patients unresponsive to other therapies may be considered for deep brain stimulation, a newer, surgical treatment option.^{42,44,47}

Clinical guidelines for the treatment of obsessive-compulsive disorder include World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for the Pharmacological Treatment of Anxiety, Obsessive-Compulsive and Post-Traumatic Stress Disorders (2008)⁴⁸, the American Academy of Child and Adolescent Psychiatry (AACAP) Practice Parameter for the Assessment and Treatment of Children and Adolescents With Obsessive-Compulsive Disorder (2012)⁴⁹, the American Psychiatric Society (APA) Practice Guideline For The Treatment Of Patients With Obsessive-Compulsive Disorder (2007)⁵⁰, and the National Institute for Health and Care Excellence (NICE) Obsessive-Compulsive Disorder and Body Dysmorphic Disorder (CG31) (2005).⁵¹ First-line treatments for mild to moderate disease include cognitive behavior therapy (CBT) or exposure and response prevention therapy (ERP). For patients with severe disease, who prefer medication or are unable to participate in psychological therapies, treatment options include treatment with an SSRI, clomipramine or combination of medication and psychological interventions. Medication, with or without psychological therapy, can be augmented if needed with SSRI, SNRI, clomipramine or more intensive psychological intervention. **Table 5** presents the clinical practice guidelines.

Table 5: Current Clinical Practice Guidelines for the Treatment of Obsessive-Compulsive Disorder

Guideline	Recommendation
<p>World Federation of Societies of Biological Psychiatry (WFSBP) (2008)⁴⁸</p>	<p>First-Line Pharmacological Treatment Recommendations</p> <ul style="list-style-type: none"> • SSRIs (escitalopram, fluvoxamine, fluoxetine, paroxetine, sertraline) <ul style="list-style-type: none"> ○ Children: Fluvoxamine, fluoxetine, paroxetine, sertraline with behavioral treatment strategies most effective • TCA clomipramine is equally effective but less well tolerated than SSRIs • Citalopram/mirtazapine were effective in double-blind, placebo controlled trials <p>Treatment Resistant Cases</p> <ul style="list-style-type: none"> • Intravenous clomipramine is more effective than oral therapy • Combination of antipsychotics (haloperidol, quetiapine, olanzapine and risperidone) with an SSRI was more effective than SSRI monotherapy • Open studies support • Studies showed success with riluzole, memantine, triptorelin, citalopram + reboxetine, clomipramine + SSRI, lithium + clomipramine, buspirone + SSRI, topiramate + SSRI, l-tryptophan + clomipramine, l-tryptophan + SSRI + pindolol <p>Efficacy results were inconsistent with MAOI phenelzine, venlafaxine, inositol Open studies demonstrate effectiveness with aripiprazole, cyproterone acetate, psilocybin and nicotine chewing gum</p>
<p>American Academy of Child and Adolescent Psychiatry (2012)⁴⁹</p>	<p>Clinicians should screen for obsessions, compulsions or repetitive behaviors</p> <ul style="list-style-type: none"> • In the presence of symptoms, perform a full evaluation using DSM-IV criteria and scalar assessment • Perform a complete psychiatric evaluation • Perform a full medical, developmental, family, school history and psychiatric history and exam <p><u>First-line treatment for mild-to-moderate cases</u></p> <ul style="list-style-type: none"> • Cognitive behavior therapy/exposure and response prevention <p><u>First-line treatment in moderate-to-severe disease</u></p> <ul style="list-style-type: none"> • Cognitive behavior therapy and medication <p><u>First-line medications</u></p> <ul style="list-style-type: none"> • Serotonin reuptake inhibitors in children • Clomipramine, sertraline, fluvoxamine, fluoxetine, paroxetine • Use according to the American Academy of Child and Adolescent Psychiatry guidelines to monitor response, tolerability and safety. <p>Selection of treatment should be guided by empirical evidence on moderators and predictors of treatment response</p> <ul style="list-style-type: none"> • Consider comorbidities, family history <p>In severe cases or those without a clinical response to CBT at several months, consider multimodal therapy (CBT and medication)</p> <ul style="list-style-type: none"> • Combined therapy yielded the best effect on symptom score and remission rate <ul style="list-style-type: none"> ○ Recommended based on a trial with sertraline, however, it is reasonable to extrapolate to any medication with efficacy in OCD <p>Medication augmentation strategies are indicated for resistant cases with moderate impairments in at least one domain of function despite adequate monotherapy</p>

Guideline	Recommendation
<p>American Psychiatric Association⁵⁰ (2007)</p>	<ul style="list-style-type: none"> • Definitions • Treatment resistant: Two medication trial failures (2 SSRIs or 1 SSRI and 1 clomipramine trial) and nonresponsive to cognitive therapy <ul style="list-style-type: none"> ○ Medication failure: 10 weeks medication at maximal or maximally tolerated doses with no change in last 3 weeks. ○ Nonresponse to cognitive therapy: <ul style="list-style-type: none"> ▪ CBT: 8-10 sessions without improvement ▪ E/RP: 6-8 sessions without improvement • Partial responders – At least 3-weeks stable, persistent (moderate or worse) OCD symptoms at a maximal SSRI dose or demonstrated a flat dose-response curve or experienced adverse effects with increased dose <ul style="list-style-type: none"> ○ Clinicians should consider: Has patient received an adequate dose trial, whether maximum dose, maximally tolerated dose and if the dosage has been stable for 3 weeks and the trial extending at least 10 weeks. <p>Medication Augmentation strategies</p> <ul style="list-style-type: none"> • Add clomipramine (25-75 mg/day) to an SSRI (most synergy documented with fluvoxamine) <ul style="list-style-type: none"> ○ Fluvoxamine inhibits clomipramine metabolism. Use of fluoxetine or paroxetine with the combination may increase clomipramine toxicity and EKG effects due to CYP2D6 inhibition. • Expert opinion: <ul style="list-style-type: none"> ○ Venlafaxine and duloxetine (inhibit monoamine uptake with fewer cardiovascular adverse effects) ○ Clonazepam and SSRIs (caution in younger children) ○ Atypical neuroleptics (based on data in adults, e.g. haloperidol, risperidone) <ul style="list-style-type: none"> ▪ May be particularly useful in the setting of tic disorders, poor insight, pervasive developmental disorder symptoms and mood instability. • Novel augmentation (not for routine use): Stimulants, gabapentin, sumatriptan, pindolol, inositol, opiates, St. John’s Wort, N-acetyl cysteine and the glutamate antagonists memantine and riluzole
	<p>PANDAS cases of OCD: Standard treatments to address both OCD and streptococcal infections</p> <p>Unproven: Therapeutic plasma exchange, intravenous immunoglobulin, D-cycloserine (effective in adults)</p> <p>Consider psychosocial treatments</p> <p>In patients with chronic tic or Tourette’s disorders, ADHD, major depression/mood disorders, bipolar disease Pharmacotherapy for comorbid disorders: Pharmacotherapy</p> <p>Psychiatric Management</p> <ul style="list-style-type: none"> • Establish a therapeutic alliance, assess symptoms, use rating scales, enhance the safety of patient and others, complete psychiatric assessment, establish goals for treatment, establish the appropriate treatment setting, enhance adherence to treatment <p>Choose Initial Treatment Modality</p>

Guideline	Recommendation
	<ul style="list-style-type: none"> • <u>First-line</u> treatment options (consider nature and severity of symptoms, co-occurring psychiatric/medical conditions and treatments, availability of CBT, past treatment history, current medications, capacities and preferences). <ul style="list-style-type: none"> ○ Cognitive behavior therapy is first-line with mild symptoms of depression, anxiety illness, willingness to do the work of CBT or the patient prefers no medication ○ SRI for those patients unable to cooperate with CBT, a history of SRI response, patient prefers SRI alone or in severe OCD where medication use may reduce symptoms allowing CBT <ul style="list-style-type: none"> ▪ In pregnancy/breast-feeding perform a risk/benefit assessment ○ Combination – unsatisfactory response to monotherapy, co-occurring psychiatric conditions where SSRIs are effective, those wishing to limit the duration of SSR <p>Choosing Pharmacotherapy</p> <ul style="list-style-type: none"> • <u>First-Line:</u> SSRIs that are FDA approved: fluoxetine, fluvoxamine, paroxetine, sertraline (via authors: citalopram and escitalopram also appear effective) <ul style="list-style-type: none"> ○ Selection should be based on safety and acceptability of side effect profile, FDA warnings, drug interaction potential, past treatment response and presence of co-occurring medical conditions. • Clomipramine (meta-analysis showed indirect superiority over SSRIs but head-to-head trials do not support this and SSRIs have fewer safety issues) <p>Choosing Psychotherapy</p> <ul style="list-style-type: none"> • Evidence is strongest for CBT with behavioral techniques (e.g. exposure and response prevention). Useful in specific settings, cognitive techniques, psychoanalysis, dynamic psychotherapy, motivational interviewing, family therapy. <p>Implementation of Pharmacotherapy</p> <ul style="list-style-type: none"> • Start with manufacturers recommended regimen. Lower initial doses if adverse effects are of concern (split tablet, liquids) • Clinical improvement begins by 4-6 weeks, may require 10-12 weeks • Up-titrate dose weekly per manufacturer recommendation for first month. Dose may be increase to maximum recommended or tolerated dose every 1-2 weeks if response is sub-optimal at 4 weeks. Continue for 6 weeks. Higher doses produce higher response rates. <ul style="list-style-type: none"> ○ Closely monitor for side effects including serotonin syndrome ○ Elderly should be started at lower doses and titrated more cautiously <p>Monitoring Adverse Events</p> <ul style="list-style-type: none"> • Regularly inquire about side effects and manage actively <ul style="list-style-type: none"> ○ Gastrointestinal distress – start with low doses and titrate slowly ○ Insomnia – add a sleep-promoting agent ○ Fatigue/sleepiness – consider modafinil ○ Sweating – low-dose anticholinergic

Guideline	Recommendation
	<ul style="list-style-type: none"> ○ Sexual effects – reduce dose, wait for symptoms to remit, try once-weekly dosing or drug holiday before sexual activity, try a different SSRI, add bupropion <p>Cognitive-Behavioral Therapies: May use individual, group, family sessions of up to 2 hours at least weekly. Twice weekly yields better results.</p> <ul style="list-style-type: none"> ● Expert consensus recommends 13-20 weekly sessions <ul style="list-style-type: none"> ○ Booster sessions if severely ill, history of relapse or with signs of relapse. Self-help treatment guides are available. <p>Lack of good response: Consider co-occurring conditions, adherence to treatment, psychosocial stress, family issues, inability to tolerate psychotherapy or maximal drug doses</p> <ul style="list-style-type: none"> ● Pharmacotherapy changes <ul style="list-style-type: none"> ○ Try alternative SSRI (venlafaxine least likely to be helpful) ○ Try switch from SSRI to mirtazapine ○ Augment with antipsychotic medication or CBT ● Consider augmentation strategies <ul style="list-style-type: none"> ○ Augment SSRIs with trials of different antipsychotic medication or CBT (using ERP) or augmenting CBT with an SSRI, add booster sessions of cognitive therapy ○ Combination SSRI/CBT reduces relapse ● Continued poor response, consider augmentation of SSRI with clomipramine (monitor central nervous system and cardiovascular side effects), buspirone, pindolol, riluzole, once-weekly oral morphine sulfate (monitor misuse), D-amphetamine, tramadol, monoamine oxidase inhibitors, ondansetron, transcranial magnetic stimulation, deep brain stimulation, intensive residential treatment/partial hospitalization, ablate neurosurgery <p>Discontinuing active treatment should be delayed 1-2 years. For most, continuation of some treatment is indicated.</p> <ul style="list-style-type: none"> ● Initiate medication discontinuation with a dose reduction of 10-25% every 1-2 months and observe for symptom recurrence/exacerbation. ● Initiate ERP discontinuation with monthly booster sessions for 3-6 months , or more intensively as indicated.
<p>National Institute for Health and Care Excellence (2005)⁵¹</p>	<p>Mild impairment or a preference against medication</p> <ul style="list-style-type: none"> ● CBT (including ERP) <p>Mild impairment in persons unable to engage in CBT (including ERP) or in which CBT has not been effective</p> <ul style="list-style-type: none"> ● SSRI (citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline) <ul style="list-style-type: none"> ○ IF partial response at 4-6 weeks, increase dose ● More intensive CBT (including ERP) <p>Moderate functional impairment</p> <ul style="list-style-type: none"> ● SSRI (citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline) <ul style="list-style-type: none"> ○ IF partial response at 4-6 weeks, increase dose ● More intensive CBT (including ERP) <p>Severe functional impairment</p> <ul style="list-style-type: none"> ● Combined SSRI and CBT (including ERP)

Guideline	Recommendation
	Do NOT use tricyclic antidepressants (except clomipramine), SSRIs, SNRIs, MAOIs, anxiolytics, antipsychotics unless the patient has comorbidities

Key: CBT = cognitive behavioral therapy, SSRI = selective serotonin reuptake inhibitor, SRI = serotonin reuptake inhibitor, ERP = exposure and response prevention therapy, SNRI = serotonin/norepinephrine reuptake inhibitor

Post-Traumatic Stress Disorder (PTSD)

Post-Traumatic Stress Disorder (PTSD) is a psychobiologic, anxiety disorder typically resulting from exposure to a trauma. Symptoms may occur acutely or be delayed in onset up to 6 months in some patients.⁵² PTSD is associated with a triad of symptoms, including 1) psychic numbing, denial or avoidance; 2) re-experiencing the traumatic event, intrusion or flashbacks; and 3) hyperarousal symptoms in the presence of distress, difficulty or impairment in daily functioning.⁵²⁻⁵⁴ Acute PTSD is defined as lasting 1-3 months following exposure to trauma while chronic PTSD continues beyond 6 months.⁵³ PTSD often presents with sleep disturbances, mood disorders, pain, somatization, substance abuse, depression, anxiety, interpersonal relationship problems and identity issues.⁵² Up to 70% of adults in the US have experienced a traumatic event. Twenty percent will go on to develop PTSD and at any given time, 8% of adults in the US have PTSD. Women are twice as likely to be diagnosed with PTSD than men. From 2012-2013, the number of PTSD cases diagnosed in military persons increased 50%. In men, the presentation relates to combat exposure and in women to sexual assault. People with PTSD are the greatest utilizers of health care, associated with a societal cost of \$42.3 billion.⁵⁵

Prevention and treatment of PTSD may include behavioral therapies and medications. Early identification and treatment may limit functional impairment although the prognosis is overall poor with up to 1/3 of persons not recovering.⁵⁶ Currently, no pharmacotherapy has shown effectiveness in preventing PTSD. Selective serotonin reuptake inhibitors (SSRIs) are first-line pharmacotherapy for PTSD. SSRIs are relatively safe medications with few adverse effects; are effective in reducing the triad of symptoms; are effective therapies for commonly associated comorbid psychiatric disorders (e.g. panic, depression, social phobia and obsessive-compulsive disorder), complicating clinical symptoms (e.g. suicidality, impulsivity, aggressive behavior) and are effective in both men and women. Other antidepressants, including tricyclic antidepressants and monoamine oxidase inhibitors (MAOIs), may be beneficial in the treatment of PTSD. Treatment with fluoxetine, sertraline and paroxetine reduced anger and irritability symptoms within one week and the triad of symptoms over 2 to 4 weeks. The choice of specific agent should be based upon the pharmacokinetics, adverse events, interactions, metabolic effects, etc. Benzodiazepines may be used adjunctively for anxiety and sleep, although dependence and worsening symptoms upon discontinuation have been reported. Other medications with limited evidence supporting their use, include second-generation antipsychotics, anticonvulsants, alpha-2 agonists and beta adrenergic blockers.⁵²

Two guidelines address the treatment of PTSD. The Australian Guidelines for the Treatment of Acute Stress Disorder & Posttraumatic Stress Disorder⁵⁷ and the VA/DoD Clinical Practice Guideline for Management of Post-Traumatic Stress⁵⁸. Guidelines do not support early, preventative therapy or use of benzodiazepines. First-line therapy includes trauma-focused cognitive behavioral therapy or eye movement desensitization and reprocessing as preferred with pharmacotherapy an option. SSRI/SNRI antidepressants are recommended. If a partial response is not due to poor adherence, treatment should continue with higher doses, an alternative

medication, combination therapy with the addition of adjunctive medications and/or enhanced psychological therapy. Non-responders should be referred to a specialist. **Table 6** presents the clinical practice guidelines.

Table 6: Current Clinical Practice Guidelines for Treatment of PTSD

Guideline	Recommendation
<p data-bbox="215 426 451 520">Australian Centre for Posttraumatic Mental Health (2013)⁵⁹</p> <p data-bbox="215 1518 451 1738">VA/DoD Clinical practice guideline for management of post-traumatic stress: The Management of PTSD Working Group (2010)^{57,58}</p>	<p data-bbox="492 426 992 453">Early Pharmacological Interventions for Adults</p> <ul data-bbox="540 459 1409 783" style="list-style-type: none"> • Medications should not be use preventively • Sleep medications (time-limited) may be used if sleep hygiene, psychological interventions are not effective. • Routine use of pharmacotherapy within 4 weeks of symptom onset is not recommended • Pharmacotherapy is indicated when distress is not managed by psychological means and a pattern of extreme hyperarousal, sleep disturbance or nightmares is present. • Consider medications if patients with a prior psychiatric history responsive to medications exhibit persistent intrusions with affective distress <p data-bbox="492 789 802 816">Pharmacologic Interventions</p> <ul data-bbox="540 823 1409 1499" style="list-style-type: none"> • <u>First-line treatment</u> remains trauma-focused cognitive behavioral therapy or eye movement desensitization and reprocessing. • <u>First-line medications</u> <ul data-bbox="638 919 1393 1205" style="list-style-type: none"> ○ Selective serotonin reuptake inhibitor antidepressants (SSRIs) <ul data-bbox="735 953 1393 1205" style="list-style-type: none"> ▪ Person unwilling or unable to engage psychological treatment ▪ Presence of concomitant condition for which SSRIs are indicated (e.g. severe depression with dissociation) ▪ Circumstances are unstable not supporting psychological treatment (e.g. ongoing domestic violence) ▪ Psychological, trauma-focus treatment has not been successful • Inadequate response to pharmacotherapy <ul data-bbox="638 1262 1349 1415" style="list-style-type: none"> ○ Consult a specialist <ul data-bbox="735 1295 1349 1415" style="list-style-type: none"> ▪ Increase current dose of medication ▪ Switch to alternative antidepressant medication ▪ Add prazosin, risperidone or olanzapine, adjunctively ▪ Reconsider psychological intervention • Continue therapy for 12 months with gradual withdrawal if responsive to treatment without significant adverse effects <p data-bbox="492 1520 607 1547">Early PTSD</p> <ul data-bbox="540 1554 1393 1881" style="list-style-type: none"> • No evidence supports early pharmacotherapy to prevent the development of PTSD <ul data-bbox="638 1619 1305 1646" style="list-style-type: none"> ○ Benzodiazepines are specifically noted to be of no benefit • <u>First-line</u> treatment options include pharmacotherapy and psychological therapy • SSRI or SNRI reassess response at 2-4 weeks. Switch to alternate if not tolerated <ul data-bbox="638 1759 1117 1881" style="list-style-type: none"> ○ Some benefit with <ul data-bbox="735 1793 1117 1881" style="list-style-type: none"> ▪ Mirtazapine ▪ Prazosin (for sleep/nightmares) ▪ Tricyclic antidepressants (TCAs)

Guideline	Recommendation
	<ul style="list-style-type: none"> ▪ Nefazodone ▪ Monoamine oxidase inhibitors (MAOIs)(phenelzine) ○ Unknown benefit with <ul style="list-style-type: none"> ▪ Atypical antipsychotic (except risperidone, as adjunct) ▪ Atypical antipsychotic (monotherapy) ▪ Conventional antipsychotics ▪ Buspirone ▪ Non-benzodiazepine hypnotics ▪ Bupropion ▪ Trazodone(adjunctive) ▪ Gabapentin ▪ Lamotrigine ▪ Propranolol ▪ Clonidine ○ No benefit with <ul style="list-style-type: none"> ▪ Benzodiazepines ▪ Tiagabine ▪ Guanfacine ▪ Valproate ▪ Topiramate ▪ Risperidone • No response to initial therapy <ul style="list-style-type: none"> ○ Assess adherence ○ Increase dose ○ Consider longer duration ○ Switch to alternate SSRI or SNRI ○ Add psychotherapy ○ Consider specialist referral • Fail second attempt at pharmacotherapy <ul style="list-style-type: none"> ○ Switch to alternate SSRI or SNRI or mirtazapine ○ Add psychotherapy ○ Augment with prazosin (sleep/nightmares)

Insomnia

Insomnia is a disorder defined by difficulty with sleep initiation, duration, consolidation, or quality.^{60,61} General insomnia disorder occurs despite adequate opportunity for sleep and results in daytime impairment and distress.^{60,61} Insomnia symptoms occur in up to half of the adult population in the United States.⁶¹ Risk factors for insomnia include increasing age, female sex, comorbid disorders, and shift work.^{60,61} It is estimated the annual cost of insomnia is over \$100 billion in the United States.⁶² In addition to the direct costs from medical treatments and prescriptions, other measurable costs of insomnia include lost productivity, accidents, hospitalizations, and comorbid conditions, such as depression due to insomnia.⁶² Early detection and intervention of insomnia can reduce the costs associated with the disorder and possibly prevent other comorbid conditions.

The medical management of insomnia includes both pharmacotherapy and behavioral therapies. Behavioral therapies include: attention to sleep hygiene, relaxation therapy, stimulus

control therapy, and sleep restriction therapy.⁶¹ A number of pharmacotherapy options exist for the treatment of insomnia including: benzodiazepines, benzodiazepine receptor agonists, ramelteon, sedating antidepressants, other sedating agents such as anticonvulsants/antipsychotic medications, or over-the-counter antihistamine and herbal drugs.⁶¹ Before the introduction of the newer benzodiazepine receptor agonist insomnia medications (zolpidem, eszopiclone, zaleplon), drug therapy for the treatment of insomnia was dominated by benzodiazepine agents due to their tolerability and rapid onset of action.^{11,61} The newer agents have a lower risk of abuse, tolerance, and dependence than the benzodiazepines and are now considered the agents of choice for treating insomnia disorder.⁶³

Clinical guidelines for the treatment of insomnia include the American College of Physicians (2016)⁶⁴ University of Texas at Austin School of Nursing, Family Nurse Practitioner Program (2014)⁵⁹ and the American Academy of Sleep Medicine (2008).⁶¹ First-line treatment strategies include sleep hygiene education, psychological or behavioral therapy. In general, first-line pharmacotherapy, includes short-to-intermediate acting benzodiazepine receptor agonists (zolpidem, eszopiclone, zaleplon, and temazepam), the selective melatonin receptor agonist, ramelteon, the tricyclic antidepressant, doxepin, and the orexin receptor antagonist, suvorexant. Pharmacological interventions lacking sufficient evidence were the benzodiazepine hypnotics (temazepam, triazolam, flurazepam, or quazepam), melatonin, trazodone as well as all complementary and alternative therapies. Options in the case of treatment failure, includes the sedating antidepressants (trazodone, mirtazapine, amitriptyline), anti-convulsants (gabapentin, tiagabine) or atypical antipsychotics (quetiapine and olanzapine). The selection of pharmacologic therapy for the treatment of insomnia includes assessment of the patient’s symptom pattern, comorbid conditions, concurrent medications, history of past treatment and responses, current treatment goals, the contraindications and side effect profile of the different agents, patient preference and cost.⁴¹ According to the newest guideline , pharmacological treatment should be at the lowest effective maintenance dosage, accompanied by patient education, and followed on a regular basis to assess for safety and effectiveness.⁶¹ **Table 7** presents the clinical practice guidelines.

Table 7: Current Clinical Practice Guidelines for the Treatment of Insomnia

Guideline	Recommendations
Management of Chronic Insomnia Disorder in Adults: A Clinical Practice Guideline From the American College of Physicians (2016) ⁶⁴	<p>All adult patients receive cognitive behavioral therapy for insomnia (CBT-I) as the initial treatment for chronic insomnia disorder</p> <p>Clinicians should use a shared decision-making approach, including a discussion of the benefits, harms, and costs of short-term use of medications, to decide whether to add pharmacological therapy in adults with chronic insomnia disorder in whom cognitive behavioral therapy for insomnia alone was unsuccessful.</p> <p>Pharmacological Treatment</p> <p>General Population</p> <ul style="list-style-type: none"> • Improved global outcomes: Eszopiclone, zolpidem (low-quality evidence) • Improved sleep outcomes: Eszopiclone, zolpidem, doxepin, (low-moderate-quality evidence) • Improved treatment response and sleep outcomes: suvorexant (moderate-quality evidence) • Ramelteon was not different than placebo (low-quality evidence) <p>Older Adults</p>

Guideline	Recommendations
	<ul style="list-style-type: none"> • Improved global and sleep: Eszopiclone (low quality evidence) • Reduced sleep onset latency: Zolpidem, ramelteon (low-quality evidence) • Improved insomnia severity index: Doxepin (moderate-quality evidence) • Improved sleep outcomes: Doxepin (low- to moderate-quality) <p>Evidence is insufficient to evaluate the balance of the benefits and harms of long-term use of pharmacologic treatments in adults with chronic insomnia disorder. FDA has approved the agents for only 4-5 weeks of therapy.</p> <p>Comparative pharmacological evidence is lacking.</p> <p>Insufficient evidence on effectiveness</p> <ul style="list-style-type: none"> • benzodiazepine hypnotics (temazepam, triazolam, flurazepam, or quazepam), melatonin, or trazodone, complimentary or alternative therapies.
<p>Clinical guideline for the treatment of primary insomnia in middle-aged and older adults (2014)⁵⁹</p>	<p>First-Line: Sleep-hygiene, psychological, behavioral therapy</p> <p>Pharmacological Therapy Evidence Support</p> <ul style="list-style-type: none"> • Level B: Ramelteon • Level C: Doxepin, non-benzodiazepine hypnotics, mirtazapine, trazodone • Level D: Antihistamines, benzodiazepines, tricyclic antidepressants (except doxepin) • Level I: Melatonin, valerian
<p>Clinical Guideline for the Evaluation and Management of Chronic Insomnia in Adults (2008)⁶¹</p>	<p>Primary Insomnia of greater than 1 month</p> <p>First-Line: Sleep-hygiene, psychological, behavioral therapy</p> <p>Pharmacological Therapy</p> <ul style="list-style-type: none"> • Short-intermediate acting benzodiazepine receptor agonists (BzRAs) <ul style="list-style-type: none"> ○ Ramelteon, zolpidem, eszopiclone, zaleplon and temazepam • Alternate short-intermediate acting BzRAs or ramelteon <p>First-line failure</p> <ul style="list-style-type: none"> • Sedating antidepressants, especially when used in conjunction with treating comorbid depression/anxiety <ul style="list-style-type: none"> ○ trazodone, amitriptyline, doxepin, and mirtazapine • Combined BzRA or ramelteon and sedating antidepressant • Other sedating agent <ul style="list-style-type: none"> ○ anti-epilepsy medications (gabapentin, tiagabine) ○ atypical antipsychotics (quetiapine and olanzapine) <p>ⓧ These medications may only be suitable for patients</p> <ul style="list-style-type: none"> • NOT Recommended: <ul style="list-style-type: none"> Over-the-counter antihistamine or antihistamine/analgesic type drugs • Valerian • Melatonin • Barbiturate or barbiturate-type drugs <p>Pharmacological treatment should be accompanied by patient education regarding:</p> <ul style="list-style-type: none"> • treatment goals and expectations • safety concerns • potential side effects and drug interactions • other treatment modalities (cognitive and behavioral treatments) • potential for dosage escalation • rebound insomnia.

Guideline	Recommendations
	<p>Patients should be followed on a regular basis</p> <p>Efforts should be made to employ the lowest effective maintenance dosage of medication and to taper medication when conditions allow. Medication tapering and discontinuation are facilitated by cognitive behavior therapy</p> <p>Chronic hypnotic medication may be indicated for long-term use in those with severe or refractory insomnia or chronic comorbid illness.</p> <p>Whenever possible, patients should receive an adequate trial of cognitive behavioral treatment during long-term pharmacotherapy.</p> <p>Long-term prescribing should be accompanied by consistent follow-up, ongoing assessment of effectiveness, monitoring for adverse effects, and evaluation for new onset or exacerbation of existing comorbid disorders</p> <p>Long-term administration may be nightly, intermittent (e.g., three nights per week), or as needed.</p>

Bipolar Disorder Disease Overview

Bipolar disorder (or manic-depressive disorder) is a mood disorder characterized by episodes of depression and mania.⁶⁵ The prevalence of bipolar disorder is 0.4 to 1.4% across the world and 4% in the US.^{9,66} In general, bipolar disorder occurs more frequently in women than men and the average age of first onset of the disease is 25 years. Bipolar disorder is the most expensive mental health disorder, costs per affected individual doubling those of depression. The economic burden of bipolar disorder in the US results from indirect costs due to lost productivity resulting from absenteeism and presentism in addition to direct healthcare costs.⁹ Bipolar disorder is also associated with an increased rate of substance abuse, legal and financial complications, relationship difficulties, self-harm and serious suicide attempts. Successful disease management and early treatment intervention can help to improve health outcomes and reduce the economic burden of bipolar disorders.⁹

The depression-mania cycles associated with bipolar disorder are unpredictable. Manic episodes typically emerge over a period of days to weeks and persist up to several weeks or months. Mania is defined as a clearly elevated mood with unrestrained behaviors lasting at least a week with at least 3 symptoms which may include irritability, grandiosity, sleeplessness, pressure talking, distractibility or engaging in activities with a high potential for adverse consequences. Clinical evidence suggests anger and agitation are the most common symptoms in pediatric patients while disordered thought content occurs most frequently in adult patients.⁶⁷ In severe mania, symptoms similar to those seen in schizophrenia, including delusions and paranoid thinking, may present. The depressive episodes are defined as a persistent low mood including lack of positive affect and anhedonia causing impairment for greater than 2 weeks. In bipolar II disorder patients may lack the full criteria for mania and the recurrent depression episodes are instead separated by hypomania episodes with mild activation and increased energy.^{13,65}

Treatment of bipolar disorder includes psychotherapy and medication therapy (mood stabilizers and antidepressant medications).^{68,69} Mood stabilizers may include lithium, anticonvulsant therapies and antipsychotic agents. Lithium is typically the first-line agent and

has demonstrated efficacy in the treatment of bipolar disorder with a response rate of 70-80%, beneficial effects within 1-2 weeks and prophylactic effects.⁶⁹⁻⁷² Antidepressants are effective in treating breakthrough depression episodes but may precipitate mania or accelerate cycle frequency. Recent clinical evidence suggests mood stabilizers demonstrating efficacy for mania are also efficacious for mixed episodes, reducing the need for antidepressant therapy.⁷³ Antipsychotic agents (such as aripiprazole, asenapine, cariprazine, lurasidone, olanzapine, quetiapine, risperidone, ziprasidone) may be used alone or in combination with other mood stabilizers or antidepressants to maintain mood stability, control agitation or treat bipolar disorder in patients experiencing loss of efficacy with lithium therapy.^{73,74}

Clinical guidelines for the treatment of bipolar disorder include the World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for Biological Treatment of Bipolar Disorder (2013)⁷⁵, the American Psychiatric Association Practice Guideline for the Treatment of Patients with Bipolar Disorder (2002)⁷⁶ the National Institute for Health and Clinical Excellence (NICE) Bipolar Disorder: The Assessment and Management of Bipolar Disorder in Adults, Children and Young People in Primary and Secondary Care (2014),⁷⁷ American Academy of Child and Adolescent Psychiatry (AACAP): Practice Parameter for the Assessment and Treatment of Children and Adolescents with Bipolar Disorder (2007),⁷⁸ the VA/DoD Clinical Practice Parameter For Management Of Bipolar Disorder In Adults (2010) and the Texas Medication Algorithm Project (TMAP) for the Treatment of Bipolar Disorder (2005). See **Table 8** for a summary of the most current guideline recommendations. In general, the guidelines recommend treatment for acute manic and acute depressive episodes and maintenance therapy in patients at high risk for recurrence or severe disease. For selection of pharmacotherapy in the treatment of acute mania or depression episodes, factors to consider include: symptoms (such as euphoric, mixed, psychotic, suicidality), severity, treatment history, adverse effect profile and patient preference.^{28,75,78,79}

Medication therapy for acute mania episodes (lithium, valproate, aripiprazole, risperidone, ziprasidone, etc.) should be continued until full remission.^{78,80,81} If no response or only a partial response is achieved after 2 weeks of therapy, increase the dose of the medication or switch to another agent. Combination therapy is recommended in patients with continued treatment-resistance to a single agent. In patients with severe mania, clozapine or electroconvulsive therapy (ECT) may be indicated. Recommendations for antidepressant therapy in the treatment of acute depression episodes are inconsistent. In general, medication therapy for acute depressive episodes (antidepressants, lithium, quetiapine, olanzapine, lamotrigine, etc.) should be provided in an established treatment setting, in combination with behavioral therapy and regularly assessed for both efficacy and adverse effects. Before initiation of treatment for acute depression, all other potential medical causes should be ruled out and caffeine, alcohol and other substances should be discontinued. Of note, the full therapeutic effects of antidepressant therapy, lithium and lamotrigine may be delayed several weeks; short-term symptomatic treatment with benzodiazepines during the first few weeks of an acute bipolar episode may be required. Maintenance therapy is recommended in patients with three or more acute episodes, two acute episodes and a positive family history for bipolar disorder or in patients with severe disease.^{69,72,75,78-80,82,83}

Table 8. Current Clinical Practice Guidelines for the Treatment of Bipolar Disorder

Guidelines	Recommendation
<p>World Federation of Societies of Biological Psychiatry (WFSBP) (2013)⁷⁵</p>	<p>Treatment of an acute mania episode, any one of the following:</p> <ul style="list-style-type: none"> • Aripiprazole 15-30 mg daily • Lithium 600-1200 mg daily (serum level 0.8-1.3 mmol, only if chronic treatment is being considered) • Risperidone 2-6 mg daily • Valproate 1200-3000 mg daily (loading dose 20-30 mg/kg; serum level 75-100 mg; not preferred in women of childbearing age) • Ziprasidone 80-160 mg daily <p>Treatment of acute depressive episode:</p> <ul style="list-style-type: none"> • Best evidence: quetiapine 300-600 mg daily • Good evidence: fluoxetine/olanzapine combination therapy • Fair evidence: bupropion, fluoxetine, imipramine, sertraline, in combination with a antimanic agent; lithium monotherapy; lithium in combination with lamotrigine, tranylcypromine, venlafaxine <p>Maintenance treatment, best evidence for:</p> <ul style="list-style-type: none"> • Aripiprazole • Lamotrigine • Lithium • Quetiapine
<p>American Psychiatric Association (APA) (2002)^{**76}</p> <p><i>**This guideline is more than 5 years old and has not yet been updated to ensure that it reflects current knowledge and practice"</i></p>	<p>Acute manic or mixed episodes</p> <ul style="list-style-type: none"> • Adjunctive antipsychotic therapy should be considered in manic or mixed manic episodes with psychotic features • Second-generation agents are recommended over first-generation agents due to side effect profile <p>Acute depressive episodes</p> <ul style="list-style-type: none"> • Adjunctive antipsychotic therapy or electroconvulsive therapy is recommended in acute depressive episodes with psychotic features <p>Maintenance</p> <ul style="list-style-type: none"> • Adjunctive antipsychotic therapy should be closely monitored, reassessed and slowly tapered, if indicated <p>Acute rapid cycling</p> <ul style="list-style-type: none"> • Combination therapy with a second-generation antipsychotic may be indicated
<p>National Institute for Health and Clinical Excellence (NICE) (2014)⁸⁰</p>	<p><u>Adults</u></p> <p>Mania</p> <ul style="list-style-type: none"> • Haloperidol, olanzapine, quetiapine or risperidone • Lithium alone or in combination with haloperidol, olanzapine, quetiapine or risperidone <p>Depression</p> <ul style="list-style-type: none"> • Fluoxetine/olanzapine, quetiapine, olanzapine, lamotrigine • Lithium alone or in combination with fluoxetine/olanzapine, quetiapine, olanzapine, lamotrigine <p>Maintenance Therapy</p> <ul style="list-style-type: none"> • Lithium alone or in combination valproate • Valproate, olanzapine, quetiapine

Guidelines	Recommendation
<p>American Academy of Child and Adolescent Psychiatry (AACAP) (2007)⁷⁸</p>	<p><u>Precautions</u></p> <p>There is an increased risk for side effects in young patients</p> <p>Antipsychotic treatment is not recommended for longer than 12 weeks in young patients</p> <p>For treatment of depression in young patients, a structured psychological intervention for at least 3 months is recommended</p> <p>Lithium and/or valproate should not be initiated in primary care</p> <p>Do not use lamotrigine for acute mania or mixed episode</p> <p>Standard therapy (based on adult literature): lithium, valproate, and/or atypical antipsychotic agents, with other adjunctive medications used as indicated; antidepressants may be used as adjunctive therapy for bipolar depression</p> <p>The choice of medication should be based on</p> <ul style="list-style-type: none"> • Evidence of efficacy • Illness phase • Presence of confounding symptoms • Side effects • Patient’s medication response history • Patient and family preferences <p>Clozapine or electroconvulsive therapy are reserved for treatment-refractory cases</p> <p>Maintenance medication therapy may be recommended to prevent relapse</p> <p>Baseline and follow-up review of symptoms/efficacy, adverse effects and laboratory monitoring is recommended</p> <p>Trial of 6 to 8-week with a mood-stabilizing agent is recommended before switching agents or adding an additional agent</p> <p>Psychotherapy is recommended as part of a comprehensive treatment plan</p>
<p>Veterans Affairs/Department of Defense (VA/DoD) (2010)⁸²(2010)</p>	<p>Mania:</p> <ul style="list-style-type: none"> • Agents most likely to be beneficial include lithium, valproate, carbamazepine, aripiprazole, olanzapine, quetiapine, risperidone or ziprasidone; lithium or valproate may be combined with an atypical antipsychotic <p>Mixed episode</p> <ul style="list-style-type: none"> • Agents most likely to be beneficial include valproate, carbamazepine, aripiprazole, olanzapine, risperidone or ziprasidone <p>Depression</p> <ul style="list-style-type: none"> • Agents most likely to be beneficial include quetiapine, lamotrigine, lithium, olanzapine/fluoxetine, olanzapine <p>Treatment response should be evaluated at 4 to 8 weeks and periodically until full remission</p> <p>Patients who have failed monotherapy for mania: consider switching to another monotherapy or combining a non-antipsychotic mood stabilizer (lithium or valproate) with a second generation antipsychotic</p>

Guidelines	Recommendation
	Treatment of severe mania or mixed episode: clozapine with valproate or lithium Treatment of severe depression: clozapine
The Texas Medication Algorithm Project (TMAP) (2005) ⁸³	<p>Hypomania Or Mania</p> <p><u>Stage 1</u></p> <ul style="list-style-type: none"> Euphoric symptoms: lithium, valproate, aripiprazole, quetiapine, risperidone, ziprasidone Mixed symptoms: valproate, aripiprazole, risperidone, ziprasidone <p><u>Stage 1b</u></p> <ul style="list-style-type: none"> Olanzapine and carbamazepine are alternatives <p><u>Stage 2</u></p> <ul style="list-style-type: none"> Combination therapy with two: lithium, valproate, olanzapine, quetiapine, risperidone, or ziprasidone (not 2 antipsychotics) <p><u>Stage 3</u></p> <ul style="list-style-type: none"> A different combination than in Stage 2, with additional options: carbamazepine, oxcarbazepine, aripiprazole, a first-generation antipsychotic <p><u>Stage 4</u></p> <ul style="list-style-type: none"> Clozapine or a 3-drug combination including lithium, an anticonvulsant mood stabilizer (valproate, carbamazepine, or oxcarbazepine) an atypical antipsychotic agent <p>DEPRESSION</p> <p><u>Stage 1</u></p> <ul style="list-style-type: none"> Lamotrigine monotherapy for patients without a recent and/or severe history of mania OR lamotrigine plus a mood stabilizer <p><u>Stage 2</u></p> <ul style="list-style-type: none"> Quetiapine monotherapy or olanzapine/fluoxetine combination treatment <p><u>Stage 3</u></p> <ul style="list-style-type: none"> Evidence-based medicine is limited

Schizophrenia

Schizophrenia is a psychiatric disorder characterized by abnormal thought processes, including delusions and hallucinations. The prevalence of schizophrenia is 0.5-1% across the world and 1.1% in the US.^{9,84} In general, schizophrenia occurs more frequently in men than women and the average age of first onset of the disease is 21-27 years. The economic burden of schizophrenia in the US (~6.85 billion in 2004) results from the combined costs associated with increased rates of unemployment, lost productivity, morbidity and mortality in addition to direct healthcare costs.⁹ Schizophrenia is associated with an increased rate of emergency department (ED) visits with almost 400,000 ED visits annually and an overall ED visit rate of 20.1 per 10,000 adults in the US. Public insurance organizations, including Medicaid and/or Medicare, are used to pay for ED visits related to schizophrenia more frequently than non-schizophrenia ED visits. Of the ED visits related to schizophrenia, about 50% result in either hospital admission (32.7%) or transfer to a psychiatric hospital (16.7%), a rate much higher than non-schizophrenia ED visits.⁸⁵ Schizophrenia is also associated with an increased risk for suicide; 33% of those diagnosed with schizophrenia will attempt suicide and up to 10% will eventually take their own lives.^{9,86} Increased understanding of the disease and improving access to mental health services improves health outcomes and reduces the economic burden of schizophrenia.

Schizophrenia is defined as a mental disorder with abnormal thought processes, irregular emotional responsiveness, delusions (false beliefs) and hallucinations (hearing or seeing things not actually present).^{9,84} Schizophrenia is a serious, chronic debilitating mental illness and the symptoms associated with the disorder make it very difficult for patients to work, form relationships or complete many daily activities of normal living. Schizophrenia symptoms are typically categorized as either “positive” symptoms or characteristics not usually seen in patients without the disorder (including delusions and hallucinations) and “negative” symptoms or characteristics lacking in patients with the disorder (including lack of motivation and social relationships and a blunted affect). Schizophrenia is a complex disorder which may be considered a collection of different disorders. According to the Diagnostic and Statistical Manual of Mental Disorders fifth edition (DSM-5), formal diagnosis of schizophrenia requires the presence of at least two symptoms for at least 1 month with continuous signs of the disease for at least 6 months.^{13,84} Patients exhibiting the symptoms of schizophrenia for less than 6 months may be diagnosed with *schizophreniform* disorder and patients with schizophrenia symptoms in combination with periods of mood disturbance may be diagnosed with *schizoaffective* disorder.¹³ Some evidence suggests full psychosis occurs later in the disease development and early, intense therapeutic interventions may reduce overall disease severity.⁸⁴

Treatment of schizophrenia may include medication therapy, psychological counseling and psychosocial interventions. Medication therapy includes antipsychotic agents, anti-anxiety medications and antidepressant therapies. Both the first-generation and second-generation antipsychotic agents have demonstrated efficacy in the treatment of schizophrenia and are the foundation of medication therapy. Unfortunately, the antipsychotic agents are also associated with numerous adverse effects, which may limit their use. For example, the first-generation agents are associated with increased rates of extrapyramidal symptoms (EPS) and the second-generation agents are associated with increased risks of metabolic adverse effects. Selection of an appropriate antipsychotic agent is based on patient-specific characteristics (age and disease severity, treatment history, comorbid conditions) and adverse event profile. In general, second-generation antipsychotic agents (such as quetiapine, risperidone, aripiprazole or ziprasidone) are recommended over the first-generation agents for first-time schizophrenia episodes due to reduced risk of neurologic adverse effects. For multiple-episode or relapse schizophrenia, treatment recommendations include increasing the dose of the current antipsychotic agent, switching to a different antipsychotic agent, assessing adherence and considering a switch to a long-acting injectable antipsychotic agent (such as olanzapine, aripiprazole, paliperidone or risperidone). Clozapine is the recommended therapy for patients with treatment-resistant schizophrenia. In general, treatment with 2 or more antipsychotic agents at the same time is not recommended and should be avoided, if possible. Benzodiazepines are recommended for treatment of schizophrenia-related agitation and antidepressants may be helpful in patients with schizophrenia and depression.⁸⁷⁻⁹²

Clinical guidelines for the treatment of schizophrenia include the World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for Biological Treatment of Schizophrenia (2012, 2013, 2015)⁸⁷⁻⁸⁹, the American Psychiatric Association Practice Guideline for the Treatment of Patients with Schizophrenia (2004)⁹³, the National Institute for Health and Clinical Excellence (NICE) Psychosis and Schizophrenia in Adults: Treatment and Management (2014)⁹⁴ and the American Academy of Child and Adolescent Psychiatry (AACAP): Practice Parameter for the Assessment and Treatment of Children and Adolescents with Schizophrenia

(2013).⁹⁵ See **Table 9** for a summary of the most current guideline recommendations. In general, the guidelines recommend treatment with a single antipsychotic agent but do not recommend one agent over another. Treatment with more than one antipsychotic agent should be avoided and clozapine is recommended in treatment-resistant schizophrenia disease. Limited evidence is available for the treatment of clozapine-resistant schizophrenia. A recent systematic review of randomized-controlled trials (2015) evaluating the efficacy of aripiprazole augmentation of clozapine, reported increased efficacy in mitigating psychotic symptoms and reduced risk of cardiometabolic and agitation/akathisia effects with clozapine and aripiprazole combination therapy.⁹⁶ A double-blind, placebo-controlled study of 40 patients with schizophrenia (2014) reported ziprasidone augmentation of clozapine significantly reduced both positive and negative symptoms on the syndrome scale and did not increase overall cardiovascular risk (QT prolongation).⁹⁷ A comparative study of ziprasidone or risperidone augmentation of clozapine (2009) reported significant psychopathological improvements compared to baseline for both ziprasidone and risperidone with differences in adverse effects between the treatment groups (increased QT prolongation and reduced extrapyramidal symptoms with ziprasidone & increased serum prolactin levels with risperidone).⁹⁸ Additional clinical evidence evaluating clozapine augmentation with risperidone, quetiapine or ziprasidone is inconsistent and suggests no added benefit with dual therapy.⁹⁹⁻¹⁰³

The Schizophrenia Patient Outcomes Research Team (PORT, updated 2009) published evidence-based treatment recommendations based primarily on empirical data, which are the basis for many of the clinical practice guidelines mentioned above.¹⁰⁴ According to the recommendations, any antipsychotic agent (with the exception of clozapine or olanzapine, due to increased risk for adverse effects with these agents) is recommended as first-line treatment of schizophrenia at daily dosages of: 300-500 mg chlorpromazine (CPZ) equivalents for all first-generation agents or on the lower end of the dose ranges for the second-generation agents. In general, the initial choice of antipsychotic medication is based on individual preference, treatment history (including efficacy, adverse effects, adherence), medical history, risk factors, concurrent medications and long-term treatment planning. For maintenance therapy, continuation of the initial agent at the effective dose or switching to a long-acting injectable (LAI) agent in patients where injectable formulations are preferred to oral formulations is recommended.

Treatment-responsive patients with an acute symptom episode generally require an increase in dose or switch to a different agent (including olanzapine). Clozapine 300-800 mg daily is recommended in patients with schizophrenia who have persistent, clinically significant positive symptoms after at least 2 trials of other antipsychotic agents, in patients who exhibit violent behaviors or in patients with suicidal thoughts or behaviors. In addition, psychosocial interventions including Assertive Community Treatment, supported employment and skills training, Cognitive Behavioral Therapy, family-based services and psychosocial interventions for tobacco, alcohol and substance use disorders demonstrate efficacy in reducing hospitalizations and homelessness in patients with schizophrenia.¹⁰⁴ A follow-up, retrospective, cohort study of the PORT recommendations in adult Medicaid beneficiaries with schizophrenia (n = 2132) was published in 2012.¹⁰⁵ According to this evidence, patients treated according to the PORT recommendations (including dose recommendations, frequent mental health visits, continuity of care) experienced reduced rates of mortality. An additional follow-up study of the PORT recommendations evaluated the rates of community mental health compliance with the PORT guidelines and reported high rates of adherence (>90%).¹⁰⁶

Table 9. Current Clinical Practice Guidelines for the Treatment of Schizophrenia

Guideline	Recommendation
<p>The Schizophrenia Patient Outcomes Research Team (PORT) (2009)¹⁰⁴</p>	<ul style="list-style-type: none"> • Treatment of Acute Positive Symptoms in Treatment-Responsive Patients: any antipsychotic agent other than clozapine with a daily dose of 300–1000 mg chlorpromazine equivalent first-generation agent OR aripiprazole 10–30mg, olanzapine 10–20 mg, paliperidone 3–15 mg, quetiapine 300–750 mg, risperidone 2– 8 mg, ziprasidone: 80–160 mg • Treatment of Acute Positive Symptoms in Patients with First-Episode Schizophrenia: any antipsychotic agent other than clozapine or olanzapine with a daily dose of 300– 500 mg chlorpromazine equivalent first-generation agent OR lower half of recommended dosage range for all second-generation agents except quetiapine (500–600 mg/day) • Maintenance Treatment in Treatment-Responsive Patients: continued agent/dose of antipsychotic treatment; long-acting injectable agents should be considered when the injectable formulation is preferred over oral therapy • Treatment of Treatment-Resistant Schizophrenia: clozapine 300-800 mg daily for at least 8 weeks is recommended in patients who continue to experience symptoms after 2 antipsychotic trials • Treatment of Special Populations: clozapine 300-800 mg daily for at least 8 weeks is recommended in patients with hostility or suicidality • Psychosocial interventions including Cognitive Behavioral Therapy and interventions for tobacco, alcohol and substance use disorders are recommended
<p>National Institute for Health and Care Excellence (NICE) (2014)⁹⁴</p>	<ul style="list-style-type: none"> • First-line recommendation: a single antipsychotic agent <ul style="list-style-type: none"> ○ Selection of antipsychotic agent should be based on patient characteristics and potential side effects ○ Large loading doses are <i>not</i> recommended ○ Combination antipsychotic therapy is <i>not</i> recommended ○ Injectable formations are recommended in patients with difficulty with adherence to oral therapy ○ Medication therapy should be continued for up to 1-2 years ○ Clozapine is recommended in patients with 2 antipsychotic trials (including one second generation antipsychotic) without significant improvement ○ The goal of medication therapy is to prevent relapse and maintain quality of life
<p>World Federation of Societies of Biological Psychiatry (WFSBP) (2012, 2013, 2015)⁸⁷⁻⁸⁹</p>	<ul style="list-style-type: none"> • Antipsychotic agents are recommended as first-line therapy in all stages of schizophrenia <ul style="list-style-type: none"> ○ Both first-generation and second-generation agents are equally effective in reducing psychotic symptoms <ul style="list-style-type: none"> ▪ Second-generation agents: olanzapine, risperidone and quetiapine have the best evidence for first-episode patients ▪ First-generation agent: haloperidol has the best evidence for first-episode patients

Guideline	Recommendation
	<ul style="list-style-type: none"> ▪ Side effects may vary between the agents and special attention should be given to motor, metabolic and cardiovascular side effects ○ Lower antipsychotic dosages are recommended in first-episode schizophrenia ○ Clozapine is not recommended for the first-line treatment in first-episode schizophrenia ○ Clozapine is recommended in treatment-resistant schizophrenia ○ Switching to another second-generation agent, preferentially olanzapine or risperidone, is recommended in clozapine-resistant schizophrenia • Limited evidence is available for the efficacy of combining two antipsychotics or an antipsychotic and another agent (mood stabilizer, anticonvulsant, etc.) in treatment-resistant schizophrenia • Psychosocial interventions are recommended along with pharmacologic treatment
<p>American Academy of Child and Adolescent Psychiatry (AACAP) (2013)⁹⁵</p>	<p>Adequate treatment of schizophrenia requires the combination of pharmacological agents and psychosocial interventions</p> <p>Pharmacotherapy:</p> <ul style="list-style-type: none"> • Antipsychotic agents are recommended for the treatment of psychotic symptoms <ul style="list-style-type: none"> ○ First-line agents include first-generation and second-generation agents <ul style="list-style-type: none"> ▪ The second-generation agents may be more helpful for negative symptoms ○ The use of an antipsychotic agent requires: <ul style="list-style-type: none"> ▪ informed consent ▪ documentation of target symptoms ▪ baseline and follow-up laboratory monitoring ▪ documentation of treatment response ▪ monitoring for known side effects ▪ adequate therapeutic trials (appropriate dose for 4-6 weeks) ○ First-episode patients should receive some maintenance treatment for 1 to 2 years ○ Some patients may benefit from the use of adjunctive agents (including antiparkinsonian agents, mood stabilizers, antidepressants, benzodiazepines) <p>Psychosocial Interventions:</p> <ul style="list-style-type: none"> • Ongoing education about the illness and treatment options • Social skills training • Relapse prevention • Basic life skills training • Problem-solving skills • Psychoeducational therapy for the family
<p>The Texas Medication Algorithm Project (TMAP) (2008)¹⁰⁷</p>	<p><u>Stage 1</u>: a low-dose second generation-agent is first-line</p> <p><u>Stage 2</u>: a trial of a single first- or second-generation antipsychotic in patients who do not respond to initial therapy</p> <p><u>Stage 3</u>: a trial of clozapine is recommended in patients without adequate response to two different antipsychotic trials or earlier in patients with a history of</p>

Guideline	Recommendation
	<p>suicidal ideation, violence or comorbid substance abuse</p> <p><u>Stage 4</u>: a trial of clozapine plus a first- or second-generation agent or electroconvulsive therapy is recommended in clozapine-resistant patients</p> <p><u>Stage 5</u>: another trial of a single first- or second-generation antipsychotic not tried in stages 1 or 2 is recommended in patients resistant to clozapine-augmented therapy</p> <p><u>Stage 6</u>: combination therapy with a first- and second-generation agent, two second-generation antipsychotics, antipsychotic therapy with electroconvulsive therapy or antipsychotic agents with mood stabilizer is recommended in patients with continued antipsychotic-resistance</p>
<p>American Psychiatric Association (APA): (2004)**93</p> <p>**"This guideline is more than 5 years old and has not yet been updated to ensure that it reflects current knowledge and practice"</p>	<ul style="list-style-type: none"> • Acute phase <ul style="list-style-type: none"> ○ First-line: aripiprazole, olanzapine, quetiapine, risperidone or ziprasidone <ul style="list-style-type: none"> ▪ Clozapine is recommended in patients with suicidal behavior, hostility or aggression ▪ A second-generation agent is recommended in patients with tardive dyskinesia or sensitive to extrapyramidal side effects <ul style="list-style-type: none"> • Only use low-dose risperidone ▪ A second-generation agent is recommended in patients sensitive to prolactin elevations <ul style="list-style-type: none"> • Not clozapine or risperidone ▪ Aripiprazole or ziprasidone is recommended in patients sensitive to weight gain, hyperglycemia or hyperlipidemia ▪ Long-acting injectable therapy is recommended in patients with non-adherence to oral therapy ○ If inadequate response, switch to a new agent: aripiprazole, clozapine, a first generation antipsychotic, olanzapine, quetiapine, risperidone or ziprasidone ○ If inadequate response to a second agent, switch again to a new agent: aripiprazole, clozapine, a first generation antipsychotic, olanzapine, quetiapine, risperidone or ziprasidone ○ Clozapine is recommended in patients with persistent psychotic symptoms ○ Consider electroconvulsive therapy for persistent severe psychosis • Stabilization or maintenance phase <ul style="list-style-type: none"> ○ Continue with acute phase pharmacological and/or electroconvulsive therapy <ul style="list-style-type: none"> ▪ If intolerable side effects, switch to a new agent: aripiprazole, a first generation antipsychotic, olanzapine, quetiapine, risperidone or ziprasidone

Diabetic Neuropathy

Diabetic neuropathy is the most common form of neuropathy and will affect 50% of diabetic patients.¹⁰⁸ Epidemiologically, from 10-100% of diabetic patients have clinical or subclinical neuropathy, while up to 50% may have asymptomatic neuropathy.^{108,109,110} The onset

of neuropathy often relates to the degree of hyperglycemia and the duration of disease.¹⁰⁸ Patients with diabetes may develop one of a number of different neuropathic syndromes defined by the portion of the nervous system affected.¹⁰⁸ Diabetic peripheral neuropathy (DPN) is associated with changes in quality of life, mobility, depression and social functioning.¹⁰⁹ The lower extremity sequelae of diabetic neuropathy include infection, ulceration and amputations.¹⁰⁸ Up to 80% of amputations are the result of a foot injury or ulcer which may have gone unnoticed and untreated in the setting of neuropathy.¹¹⁰ Treatment is directed toward reducing pain, and improving quality of life.¹⁰⁹

Pharmacological treatment of diabetic neuropathy first includes the exclusion of other etiologies.¹⁰⁸ Only improving glycemic control and avoiding large glucose excursions has been shown to prevent or delay the development of DPN in type I diabetics, and slow progression in type 2 diabetes.¹⁰⁹ Treatment includes the use of antidepressants, anticonvulsants, opioids (including dextromethorphan, tramadol) and combination therapies. Other, unproven interventions include acetyl-L-carnitine, isosorbide and non-steroidal anti-inflammatory drugs. Non-pharmacological interventions include electrical nerve and spinal cord stimulation.

Clinical guidelines for the treatment of diabetic neuropathic pain include the joint American Academy of Neurology, American Association of Neuromuscular and Electrodiagnostic Medicine and American Academy of Physical Medicine and Rehabilitation Evidence-Based Guideline: Treatment of Painful Diabetic Neuropathy¹¹¹, the National Institute for Health and Care Excellence Neuropathic Pain in Adults: Pharmacological Management in Non-Specialist Settings guideline¹¹², the American Diabetes Association Clinical Practice recommendations¹⁰⁹ and the Canadian Diabetes Association Guideline^{113,114}. Anticonvulsants may provide the best response to therapy with pregabalin having the highest strength evidence supporting its use. Other anticonvulsants supported by evidence include gabapentin and valproate. Antidepressants which have proven utility include amitriptyline, venlafaxine and duloxetine. Recommended opioids include tramadol, morphine, oxycodone controlled release, tapentadol and dextromethorphan. Local relief may be obtained with topical capsaicin (not patch) or nitrate spray. See table 10 for a list of the most current guideline recommendations.

Table 10: Current Clinical Practice Guideline for the Treatment of Diabetic Peripheral Neuropathy

Guideline	Recommendations
American Academy of Neurology, the American Association of Neuromuscular and Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation (2011) ¹¹¹	Pharmacological Therapies Anticonvulsants <ul style="list-style-type: none"> • Level A: Pregabalin • Level B: Gabapentin and sodium valproate <ul style="list-style-type: none"> ○ Valproate caution: women of childbearing age, glycemic control, weight gain • Level B: Oxcarbazepine, lamotrigine and lacosamide are NOT recommended • Level U: Insufficient Evidence: Topiramate • Level B: Probably effective; venlafaxine, duloxetine, amitriptyline, gabapentin, valproate, opioids (morphine, tramadol, oxycodone controlled release), capsaicin Antidepressants <ul style="list-style-type: none"> • Level B: Amitriptyline, venlafaxine, duloxetine • Level C: Venlafaxine added to gabapentin may improve response

Guideline	Recommendations
	<ul style="list-style-type: none"> Level U: insufficient evidence for desipramine, imipramine, fluoxetine or combination therapy with nortriptyline and fluphenazine <p>Opioids</p> <ul style="list-style-type: none"> Level B: Dextromethorphan, morphine, tramadol and oxycodone controlled release <p>Other Pharmacological Agents</p> <ul style="list-style-type: none"> Level B: Capsaicin and isosorbide dinitrate spray Level B: Clonidine, pentoxifylline and mexiletine are NOT recommended Level C: Lidoderm patch may be considered Level U: Vitamins or α-lipoic acid <p>Recommended Dosing</p> <ul style="list-style-type: none"> Pregabalin 300-600 mg/day; Gabapentin 900-3600 mg/day; Sodium valproate 500-1200 mg/day; Venlafaxine 75-225 mg/day; Duloxetine 60-120 mg/day; Amitriptyline 25-100 mg/day; Dextromethorphan 400 mg/day; Morphine (titrated) 120 mg/day; Tramadol 210 mg/day; Oxycodone, mean 37 mg/day, max 120 mg/day; Capsaicin, 0.075% QID; Isosorbide dinitrate spray
National Institute for Health and Care Excellence [CG173] (2013) ¹¹²	<p>Pharmacological Interventions (all neuropathic pain except trigeminal neuralgia)</p> <ul style="list-style-type: none"> Initial therapies include duloxetine, gabapentin, pregabalin Try another agent (or both) if a patient fails initial therapy Tramadol is recommended only for acute rescue therapy Capsaicin cream may be used for localized pain when patients prefer topical treatment or are intolerant of oral therapy Do NOT use (unless advised by a specialist) <p>Cannabis, capsaicin patch, lacosamide, lamotrigine, levetiracetam, morphine, oxcarbazepine, topiramate, tramadol (except acute, short-term use), venlafaxine</p>
American Diabetes Association (2015) ¹⁰⁹	<p>Optimize glucose control (prevent wide excursions)</p> <ul style="list-style-type: none"> Acceptable therapy includes, pregabalin, duloxetine, tapentadol, venlafaxine, amitriptyline, gabapentin, valproate, morphine, tramadol, oxycodone controlled release Pharmacotherapy does not provide complete pain relief
Canadian Diabetes Association (2013) ¹¹⁴	<p>Treat with intensified glycemic control</p> <p>Anticonvulsants</p> <ul style="list-style-type: none"> Grade A: Pregabalin Grade B: Gabapentin, valproate <p>Antidepressants</p> <ul style="list-style-type: none"> Grade B: Amitriptyline, duloxetine, venlafaxine <p>Analgesics</p> <ul style="list-style-type: none"> Grade B: Tapentadol ER, oxycodone ER, tramadol Grade B: Topical nitrate spray

Key: Level A/Grade A-Strong evidence; Level B/Grade B-Moderate evidence; Level C-Weak evidence; Level U-Insufficient evidence; QID-four times a day; ER-extended-release

Pharmacology

Mechanism of Action

Tricyclic antidepressants are categorized by their chemical structure. Tertiary amine tricyclic agents (amitriptyline, clomipramine, doxepin, imipramine and trimipramine) block serotonin reuptake. The secondary amine tricyclic (desipramine, nortriptyline, protriptyline) and tetracyclic amine compounds (amoxapine, maprotiline) were developed to minimize the side effects associated with the first-generation agents.^{1,115} Tertiary amine tricyclic compounds are more potent serotonin receptor blocking agents, whereas the secondary amine tricyclics more potently block the norepinephrine receptor.¹ The tertiary amines, amitriptyline, clomipramine and imipramine undergo demethylation to secondary amines and exert both serotonergic and norepinephrine effects.¹

The mechanism of antidepressant action of TCAs has not been fully determined. Beyond the direct effects on serotonin and norepinephrine receptors, activity may relate to postsynaptic signal transduction, neurotrophic factors, gene expression or other mechanisms.^{1,115-117}

Additionally, TCAs exhibit activity at other receptors.^{1,2,117,118} Activity at the muscarinic, histamine, α_1 -receptor and fast sodium channels are responsible for many of the side effects of the TCAs. Muscarinic receptor blockade produces anticholinergic side effects (e.g. dry mouth, constipation, blurred vision, drowsiness, sedation, hallucinations, memory impairment, urinary retention, etc.). Histamine-1 receptor (H_1) blockade produces antihistaminic effects (e.g. sedation, delirium, increased appetite and weight gain). Tricyclics inhibit α_1 neuro-transmission (e.g. orthostatic effects and tachycardia). TCAs act on fast sodium channels by inhibiting Na^+/K^+ -ATPase resulting in conduction delays. Ventricular effects are more pronounced, giving these agents type-I antiarrhythmic or quinidine-like activity.^{1,116}

Pharmacokinetics

TCAs are lipophilic, highly protein bound and exhibit a large volume of distribution.^{1,4-6,117,119} Peak TCA levels are achieved within 2 to 8 hours after ingestion. The anticholinergic effects of these drugs slow gastric emptying which may result in erratic absorption and varied onset of action in some patients.^{120,121} The agents undergo first-pass metabolism in the liver with tetracyclic compounds hepatically cleared. Metabolism occurs by two mechanisms. Tertiary amines are metabolized to secondary amines by demethylation and hydroxylation of the ring structure produces hydroxyl compounds that are further conjugated and eliminated. The half-life for most agents is greater than 12 hours allowing for once daily bedtime dosing to accommodate their sedative properties.^{29,122} Treatment of depression should continue 4-8 weeks to determine if patients are responders, partial-responders or nonresponders. Likewise, an assessment of effectiveness in migraine prophylaxis requires a trial of 8-12 weeks and for TCA-induced analgesia a treatment duration of 1-3 weeks.¹²³⁻¹²⁵

The TCAs are metabolized through a variety of hepatic microsomal enzymes including CYP2D6, CYP1A2, CYP 3A4, and CYP2C19.¹ Genetic variability in these enzymes may affect serum concentrations.²⁹ Desipramine displays nonlinear kinetics within the normal dosing range. **Table 11** compares the pharmacokinetics of the TCAs.

Table 11: Pharmacokinetics of TCAs

	Absorption	Distribution	Metabolism Active Metabolite	Excretion	Elimination Half-life
Amitriptyline	Rapid, well absorbed BA: 43 to 46% Tmax: 2 to 5 hours	PB: > 90% Vd: 18 to 22 L	N-demethylation Active: nortriptyline Inactive: Hydroxy- and conjugated derivatives	Renal: Major (metabolites), 18% unchanged Fecal: Minor	13-36 hours
Amoxapine	Rapid and well absorbed Tmax: 90 minutes Onset of action: 1 to 2 weeks up to 4 to 6 weeks	Vd: 0.9 to 1.2 L/kg PB: 90%	Hepatic hydroxylation Active: 7-hydroxyamoxapine (7-OH-amoxapine) and 8-hydroxyamoxapine (8-OH-amoxapine) Metabolites further conjugated to glucuronides	Renal	Amoxapine: 8 hours 8-hydroxyamoxapine metabolite: 30 hours
Clomipramine	BA: 20 to 78% Onset of action: 1 to 2 weeks; Max at 8 to 12 weeks Duration of action: 1-2 days CSF:Plasma ratio 2.6 Tmax: 2 to 6 hours	Vd: 12 L/kg PB: 97%	Extensive first-pass metabolism Active: desmethyl-clomipramine (DMI) Further conjugated to glucuronides Metabolism may be non-linear Concentrations of DMI > clomipramine	Renal: 50-60% Fecal: 24% to 32%	Clomipramine: 19 to 37 hours DMI: 54-77 hours Half-life is longer with higher doses
Desipramine	Rapid absorption Tmax: 6 hours Onset of action: 4 to 8 weeks	Vd: 33 to 44 L/kg	Extensive first-pass metabolism Active: 2-hydroxydesipramine	Renal: 70%	15-24 hours
Doxepin	Tmax: 3.5 hours Tmax, Silenor: 3.5 hours Food: ↑ AUC 41%; ↑ Cmax 15%; Tmax delayed Onset of action:	Vd: 20 L PB: 80% Silenor: 11,930 L	CYP2C19; CYP2D6 Active: N-desmethyldoxepin (nordoxepin)	Renal: Major	Doxepin hydrochloride: 15.3 hr Desmethyldoxepin: 31 hr

	Absorption	Distribution	Metabolism Active Metabolite	Excretion	Elimination Half-life
	Depression: 4 to 8 weeks Anxiety: 2 to 6 weeks				
Imipramine	BA: 22 to 77% Tmax: 2 to 6 hours Onset of Action: 4 to 8 weeks	Vd: 14.5 L/kg children Vd: 10-20 L/kg adults PB 60 to 96%	Significant first-pass effect CYP2D6 Active: desipramine	Renal: Major	8 to 21 hours Mean: children 11 hours Mean: adults 16-17 hours Desipramine: 22-28 hours
Maprotiline	BA: 65 to 72% Absorption: 100% Tmax: 8 to 24 hours Onset of action: 4 to 8 weeks	Vd: 22.6 L/kg PB 88%	N-demethylation, oxidative deamination, and aliphatic and aromatic hydroxylation Active and inactive metabolites	Renal: 70% Fecal: 30%	28 to 105 hours
Nortriptyline	Tmax: 7 to 8.5 hours Onset of action: 7 to 21 days; up to 3 weeks	Vd: 14-22 L/kg PB: 93-95%	Extensive first-pass metabolism	Renal: Primary Fecal: Minor	Children: 14 to 22 4 hours Adults: 28 to 31 hours
Protriptyline	Rapid, complete absorption Tmax: 6 to 12 hours Duration of action: 1 to 2 days	Vd: 15 to 31 L/kg PB: High	First-pass effect: 10-25% N-oxidation, hydroxylation, glucuronidation	Renal	54 to 92 hours
Trimipramine	BA: 18 to 63% Tmax: 1 to 6 hours	Vd: ~ 30 L/kg PB: 95%	Extensive first-pass effect Active: Desmethyltrimipramine	Renal	7 to 40 hours

Key: BA-bioavailability; Tmax-time to maximum concentration; Vd-volume of distribution; PB-protein binding; CSF-cerebrospinal fluid

Special Populations: ⁴⁻⁶ (See Table 12)

Pediatrics: Desipramine, maprotiline, nortriptyline, protriptyline and trimipramine are not indicated in children or adolescents. Pediatric dosing is established in children ≥ 6 years of age with imipramine, ≥ 10 years of age with clomipramine, ≥ 12 years of age for amitriptyline and doxepin and at ≥ 16 years of age with amoxapine. Higher dosages are often used in children as they display more rapid metabolism and clearance of TCAs.¹ For instance, clomipramine use in younger patients results in a lower plasma-concentration-per-equivalent-dose ratio than adults.

Geriatrics: The American Geriatric Society Beers Criteria for Inappropriate Medication Use in Older Adults recommends TCA use be avoided.¹²⁶ Amoxapine, desipramine, nortriptyline and protriptyline cause more problematic anticholinergic side effects in the elderly. Sedation and orthostatic hypotension are more common in the elderly although tolerance often develops to the TCA hypnotic effects.⁴ Low dose doxepin (≤ 6 mg/day) is considered safe for use in the elderly.¹²⁶ When TCAs are prescribed in the elderly, lower starting doses are recommended for all TCAs except clomipramine, secondary to reduced drug clearance.^{1,4} Additionally, geriatric patients are at increased risk of hyponatremia or the syndrome of inappropriate antidiuretic hormone secretion.⁴

Pregnancy/Breast Feeding: Maprotiline carries an FDA pregnancy category B rating. Other agents are category C with the exception of imipramine, nortriptyline and protriptyline for which there is no US assignment and for which a consideration of the risk-benefit of therapy is recommended. Prescribers are encouraged to enroll every pregnant woman receiving these agents in the National Pregnancy Registry for Antidepressants (<https://womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry/>). As a class, these agents do cross into breast milk, however, a risk-benefit assessment for use during breastfeeding is recommended.

Hepatic impairment: A reduced dose of Silenor® (doxepin) is recommended in patients with hepatic dysfunction. Other agents recommend cautious use without specific dosing adjustments. Hepatic metabolism is affected by genetic variation. Poor metabolizers may exhibit higher serum concentrations of TCAs. This includes 5-10% of Caucasians via reduced CYP2D6 metabolism and 20% of Asians via poor CYP2C19 metabolism. Additionally, smoking induces hepatic microsomal enzymes and results in lower serum levels of clomipramine and desipramine.⁵

Renal impairment: Dosing adjustments are not required for use in renal dysfunction, however, caution is advised.

Cardiovascular disease: TCAs exert quinidine-like effects, prolong the PR and QTc intervals, delay intraventricular conduction and induce sinus tachycardia. Risk factors for ventricular arrhythmias, include concomitant cardiodepressant medications, underlying bundle branch block, preexisting conduction delays, other cardiac disease receive high doses of TCAs or have a baseline QTc interval of ≥ 450 msec. Children with immature conduction systems may be at arrhythmogenic risk. Sudden cardiac death is possible in patients with underlying ischemic heart disease.¹

Genetic Effects: Hepatic microsomal enzyme activity differs among genetic populations. CYP3A4 metabolism is more rapid in Swedes who are considered “ultrametabolizers”.¹²⁷

Table 12: Special Populations

	Renal Dysfunction	Hepatic Dysfunction	Pregnancy	Lactation (Excreted into breast milk)	Pediatric	Geriatric
Amitriptyline	No recommendations: Use with caution	Use with caution (hepatically eliminated)	C	Yes Consider the risk/benefit of therapy	Age < 12 years: Not established	Lower doses are recommended: 10 mg 3 times daily and 20 mg at bedtime
Amoxapine	No recommendations: Use with caution (renally eliminated)	No recommendations	C	Yes Consider the risk/benefit of therapy	Age < 16 years: Not established	Begin with lower doses: 25 mg 2 to 3 times daily. Based on response and tolerability dose may be increased after 7 days to 50 mg 2 to 3 times daily. Usual effective dose is 100 to 150 mg daily Max: 300 mg daily
Clomipramine	Not studied: Use caution with significant renal dysfunction	Use caution (not studied)	C	Yes Consider the risk/benefit of therapy	Age < 10 years: Not established	Usual adult dosing
Desipramine	No recommendations	No recommendations	C	Yes Consider the risk/benefit of therapy	Not established	Begin with lower doses and titrate based on response and tolerability to maintenance dose Maintenance Dose: 25 to 100 mg in single or divided doses daily Max dose: 150 mg daily
Doxepin	No recommendations	Silenor: <ul style="list-style-type: none">Initiate therapy with 3 mg daily	C	Yes Use with caution Apnea and drowsiness reported	Age < 12 years: Not established	Begin with lower doses, observe closely Use once daily dosing Max: 6 mg daily
Imipramine	No recommendations (use with caution)	No recommendations (use with caution)	**	Nursing is not recommended	Age < 6 years: Not established	Begin with lower doses: 25 to 50 mg at bedtime; if tolerated increase every 7 days for outpatients

	Renal Dysfunction	Hepatic Dysfunction	Pregnancy	Lactation (Excreted into breast milk)	Pediatric	Geriatric
						Max: 100 mg daily
Maprotiline	No recommendations	No recommendations	B	Yes Consider the risk/benefit of therapy	Not established	Begin with lower doses: 25 mg daily; based on response and tolerability increase dose by 25 mg every 2 weeks Usual dose: 50 to 75 mg daily in divided doses or once daily
Nortriptyline	No recommendations	Lower and slower dosing is recommended	**	Yes Monitoring recommended	Not established (dosage regimens given for adolescents)	Begin with lower doses: 30 to 50 mg daily as single or divided doses
Protriptyline	No recommendations	No recommendations	**	Unknown Consider the risk/benefit of therapy	Not established	Begin with lower doses: 15 mg daily in 3 divided doses; gradually increase based on response and tolerability Max: 60 mg daily Doses > 20 mg daily require close monitoring of cardiovascular system
Trimipramine	No recommendations	No recommendations	C**	Unknown but likely Consider the risk/benefit of therapy	Not established	Begin with lower doses: 50 mg daily at bedtime; titrate dose based on response and tolerability Usual dose: 100 mg at bedtime Maintenance: Titrate to lowest effective dose gradually increase dose based on response and tolerability to 100 mg daily. Maintenance: Lowest effective dose at bedtime

Key: * = Pregnant women, 18 to 45 years of age, receiving antidepressants are encouraged to enroll in the National Pregnancy Registry for Antidepressants (NPRAD) as early in pregnancy as possible; ** = No US assignment, inconclusive results, consider risk-benefit of therapy; LFTs = liver function tests; ESRD = end-stage renal disease

Methods

A literature search was conducted to identify articles addressing each key question, searching the MEDLINE database, EMBASE, the Cochrane Library and reference lists of review articles. For the clinical efficacy section, only clinical trials published in English and indexed on MEDLINE or EMBASE, evaluating efficacy of the tricyclic/tetracyclic antidepressants are included. Trials evaluating the agents as monotherapy or combination therapy where adjunctive medications remained constant throughout the trial are included. Non-comparative and placebo-controlled trials and trials comparing monotherapy with combination regimens are generally excluded.

Clinical Evidence

Evidence for tricyclic antidepressants was found for a number of indications, including unipolar major depressive disorder, depression in the physically ill, for amitriptyline, depressed elderly, maintenance therapy in the depressed elderly, children and adolescents, depression in cancer, low vs standard tricyclic dosing, nocturnal enuresis, pain in rheumatoid arthritis, fibromyalgia, neuropathic pain, tension headache, migraine prophylaxis, attention-deficit hyperactivity disorder, autism spectrum disorder and irritable bowel syndrome. In general, clinical evidence is of low quality and hampered by a number of issues.¹²⁸ TCAs are an older class of medications. Most studies were performed prior to an emphasis on methodology. Antidepressant therapy is associated with a significant placebo effect.¹²⁹ Most studies are efficacy and not effectiveness trials limiting extrapolation to the average patient. Patients with comorbidities were most often excluded from trials. Methodological deficiencies were common and direct comparative evidence is overall lacking.

Unipolar Major Depressive Disorder: A Cochrane review¹³⁰ evaluated fluoxetine and other antidepressants in the treatment of adults with unipolar major depressive disorder. No differences in efficacy were found between fluoxetine and the TCA class for 50% HAM-D response (OR 0.97; 95% CI 0.77-1.22; 24 RCTs; N=2124) or for individual TCAs. Dropout rate were lower for fluoxetine than TCAs (OR 0.79; 95% CI 0.65-0.96; NNT=20; 95% CI 13 to 48; 49 RCTs; N=4194) and fluoxetine was better tolerated than amitriptyline (dropout OR 0.62; 95% CI 0.46-0.85; NNT=13, 95% CI 8-39, 18 RCTs, N=1089). Dropout rates due to adverse events were lower with fluoxetine therapy amitriptyline (OR 0.41; 95% CI 0.23-0.71; NNT=12; 95% CI 8 to 22; 16 RCTs, N=1038), clomipramine (OR 0.30; 95% CI 0.12 to 0.79; NNT=11; 95% CI 6 to 46; 2 RCTs, N=163), imipramine (OR 0.47; 95% CI 0.26 to 0.86; NNT= 8; 95% CI 6 to 12; 10 RCTs; N=1093) and overall TCAs (OR 0.55; 95% CI 0.40 to 0.75; NNT=14; 95% CI 10 to 20; 40 RCTs; N=3647).

Assessment: Methodological limitations yield low-quality evidence that found no difference in efficacy between fluoxetine and the TCA class or individual agents (amitriptyline, clomipramine or imipramine). Fluoxetine was better tolerated than the TCAs with fewer dropout rates and superior compared to individual TCAs (amitriptyline, clomipramine, imipramine) for dropouts due to adverse effects.

Physically-Ill Depressed: A Cochrane Review¹³¹ evaluated the use of antidepressants in physically ill depressed patients. Efficacy was assessed from 44 trials of 3372 participants. Included were studies using any antidepressant. TCA studies included nortriptyline (N=4), desipramine (N=3) and imipramine (N=2). Subgroup analysis specifically compared SSRIs and

TCAs to placebo. The pooled antidepressants efficacy analysis found improvements in depressive symptoms at 6-8 weeks favored antidepressant therapy over placebo, OR 2.33 (95% CI 1.80-3.00; $p < 0.00001$; 25 studies; N=1674 patients). Subgroup analysis found tricyclic antidepressants and SSRIs reduced depressive symptoms more than placebo at 4-5 weeks. Efficacy for TCAs but not SSRIs was statistically superior to placebo at 4-5 weeks, TCAs with an OR of 4.79 (95% CI 1.86-12.37; $p = 0.001$; 3 trials; N= 95) and SSRIs with an OR of 2.08 (95% CI 0.75-5.76; $p = 0.16$). At 6-8 weeks the odds ratio of response was higher with TCA (OR 3.85; 95% CI 1.88-7.87; $p = 0.0002$; 7 studies; N=337) than SSRI therapy (OR 1.92; 95% CI 1.48-2.49; $p < 0.00001$; 16 studies; N=1135) although both were statistically superior to placebo. At 9-18 weeks, both classes of antidepressants performed well, with wide confidence intervals favoring SSRI therapy. No medication specific subgroup analysis was performed. Dropout rates for both SSRIs and TCAs were higher than placebo over the first 9 weeks. After 9 weeks, the dropout rates did not differ between treatments and placebo. Adverse events more common with treatment than placebo and for SSRI therapy, included dry mouth and sexual dysfunction, while TCA therapy was associated with more dry mouth.

Assessment: Included for place in therapy. Although reporting biases may have exaggerated the size of response, it appears that TCAs and SSRIs offer at least comparable efficacy in the setting of physically-ill depressed patients. TCAs may afford an earlier response than SSRI but further evidence is needed to confirm this finding.

Depression, Amitriptyline: One Cochrane Review evaluated the comparative efficacy and tolerability of amitriptyline for depression. The Cochrane Review¹³² compared treatment of depression with amitriptyline to other tricyclic, heterocyclics and SSRI antidepressants. Analysis of 194 studies found amitriptyline performed statistically, but not likely clinically, better than the comparators group for outcomes of efficacy and effect size. This finding was consistent when amitriptyline was compared to the entire comparator group or just SSRIs. No comparison between amitriptyline and other TCAs was performed. Although dropout rates were similar across comparisons, amitriptyline was associated with a significantly higher side effect rate (OR 0.66; 95% CI 0.59- 0.74) than the grouped comparators. Tolerability analysis for amitriptyline found the number needed to treat to harm equaled 40. Overall, amitriptyline was as effective as other antidepressants but associated with a larger risk profile.

Assessment: Clinical efficacy of amitriptyline in depression was statistically superior although not clinically superior to grouped comparators (SSRIs, tricyclic and tetracyclic antidepressants) with more adverse events and lower tolerability.

Depressed Elderly: Two meta-analysis compared the effects of antidepressants in the depressed elderly. One meta-analysis¹³³ in moderately to severely depressed patients 60 years and older found no difference in the ability of TCAs, SSRIs or atypical antidepressants to reduce depressive symptoms. The response rate for TCAs was 63.1% (95% CI: 57.4-76.7) for SSRIs 57.7% (95% CI: 45.5-69.8) and for atypical antidepressants 33.4% (95% confidence interval, CI: 5.2-61.7)). The pooled difference in efficacy was greater with SSRIs than atypical antidepressants, -36.9% (95% CI: -65.4, -8.4, $p = 0.01$) but comparable between SSRIs and TCAs. The rate of adverse events was similar between TCAs (60.3%); and SSRIs (59.1%) and higher

than with atypical (11.2%) or placebo (25.6%) therapy. Dropout rates did not differ significantly between groups (TCAs 23.2%; SSRIs 18.5%; Atypicals 11.2%; Placebo 25.6%).

A second meta-analysis¹³⁴ compared the efficacy and tolerability of pharmacological and psychological interventions in the treatment of elderly depression (age > 55 years). The meta-analysis included 41 trials which included TCAs (N=30), SSRIs (N=16) and various other antidepressants (N=35). The percent decline in HAM-D scores was significantly greater for all pharmacotherapy vs. placebo (weighted sample size analysis 48% vs 31.3%; unweighted 50.6% vs 21.4%). Subset analysis of 13 placebo controlled trials found a significant difference between SSRIs and TCAs ($F=4.70$, $df=2,19$, $p=0.32$; weighted analysis) for HAM-D reduction between SSRIs and TCAs (35% vs 50% respectively) Tolerability, defined as dropouts or dropouts due to adverse events was not different between SSRIs and TCAs. No single antidepressant class demonstrated superiority in efficacy although direct comparative data is lacking.

Assessment: Included for place in therapy. The analyses were limited by heterogeneity, power and robustness. Antidepressants are more efficacious than placebo in the treatment of the depressed elderly with no significant differences found between antidepressant classes. Efficacy may be greater with SSRIs and TCAs than atypical antidepressants although adverse events are less common with atypical antidepressants but further evidence is needed to confirm these findings.

Depression Elderly, Maintenance Therapy: A Cochrane Review¹³⁵ evaluated continuation and maintenance antidepressant therapy in older adults with depression. Included were 7 trials involving 803 participants. Two trials evaluated psychotherapeutic interventions, 3 trials TCAs and 3 trials SSRI antidepressants. Meta-analysis evaluated outcomes of recurrence at 6 months, 12 months, 24 months and 36 months for antidepressant therapy vs placebo. Evidence indicated antidepressant therapy was ineffective to reduce recurrence of depression at the 6-month or 24-month followup periods. A statistically significant reduction in recurrence was noted at 12-month assessment in 3 trials of 247 participants, RR 0.67 (0.55-0.82; number needed to benefit, NNTB=5) favoring antidepressant therapy. At 24-months, pooled antidepressant data found inefficacy, however when TCAs were assessed separately a significant benefit in reducing recurrence was noted (three RCTs; N=169; RR = 0.70, 95% CI 0.50-0.99; NNTB=5). At 36 months, 1 trial (N=123) comparing combination psychological and nortriptyline therapy found a statistically significant reduction in relapse recurrence rate (N = 54, RR = 0.36, 95% CI 0.20 to 0.64) with combination therapy.

Assessment: Included for place in therapy. Tricyclic antidepressants appear to be more efficacious than SSRIs and placebo in preventing recurrence during maintenance therapy than SSRIs.

Children and Adolescents: Two Cochrane Reviews evaluated the use of TCAs in children and adolescents. The first review¹³⁶ evaluated the use of TCAs in the treatment of depression. Included were 14 trials involving 590 participants. Treatment with a TCA did not improve remission rates, depression symptom scores or clinical global assessment scores. Compared with placebo therapy, TCAs produced a higher incidence of vertigo, orthostatic, hypotension, tremor and dry mouth. Discontinuation rates did not differ between groups. Subset analysis found no difference in outcomes or tolerability when children and adolescent data was assessed separately. The second review¹³⁷ evaluated pharmacotherapy for anxiety disorders. Included were 22 trials

involving 2519 participants. A single TCA trial was found comparing desipramine to clomipramine. Data was insufficient for inclusion in meta-analysis.

Assessment: Evidence does not support the use of TCAs in the treatment of depression in young people. Evidence is lacking to assess the efficacy of TCA therapy in children and adolescents with anxiety disorders.

Depression, Cancer: One Cochrane Review¹³⁸ evaluated the use of TCAs in the treatment of depression associated with cancer. Nine studies of 861 participants were identified. Very low quality evidence found antidepressant therapy improved continuous outcome measures of depression via Hamilton Rating Scale for Depression (HRSD), Montgomery and Åsberg Depression Rating Scale (MADRS) or Clinical Global Impression Rating scale (CGI). Evidence of differences between antidepressant therapy and placebo was scarce. Three trials (N = 237) included in the analysis found very low quality head-to-head evidence that SSRIs and TCAs are not different in efficacy by analysis of (SMD -0.08, 95% CI -0.34-0.18). Evidence is insufficient to promote antidepressant therapy and treatment of a depressed person with cancer should be individualized.

Assessment: Evidence is lacking to support the use of TCAs or any specific TCA in the treatment of depression associated with cancer.

TCA Dosing: A single meta-analysis compared low dose (<100 mg daily) to standard dose tricyclic therapy (amitriptyline, clomipramine, desipramine, doxepin, trimipramine) in the treatment of acute depression. Furukawa et al¹³⁹ included 35 studies involving 2013 participants in the analysis. Low-dose tricyclic therapy resulted in effectiveness superior to placebo at 6-8 weeks (OR 1.47, 95% CI 1.12-1.94) and not different than standard-dose therapy (relative risk, RR 1.11; 95% CI 0.76-1.61). Standard- and low-dose therapy did not differ in improving depressive symptoms although standard-dose therapy was associated with more withdrawals due to adverse events.

Assessment: The use of low- vs standard-dose amitriptyline, clomipramine, desipramine, doxepin and trimipramine resulted in similar effectiveness in the treatment of depression with fewer adverse events. Individual comparative analysis was not performed.

Nocturnal Enuresis: A Cochrane Review¹⁴⁰ of desmopressin for nocturnal enuresis in children identified 5 trials comparing desmopressin to amitriptyline or imipramine. Trial sizes were too small to give definitive results. Overall, each medication was efficacious. Desmopressin therapy was associated with a higher cost, while use of TCAs resulted in more adverse events. An updated and expanded Cochrane Review¹⁴¹ by the same authors found no additional evidence.

Assessment: Although the amitriptyline, imipramine and desmopressin were all modestly efficacious in nocturnal enuresis, the evidence is weak and further evidence is needed.

Rheumatoid Arthritis Pain: A Cochrane review¹⁴² evaluated the benefit of antidepressant use in the treatment of Rheumatoid Arthritis pain. A total of 8 trials were included. Medications included amitriptyline, imipramine, desipramine, trimipramine, dothiepin, d-propoxyphene, paroxetine and trazodone. The only head-to-head trial was of paroxetine and amitriptyline. Analysis of the trials found insufficient evidence to support the use of any antidepressant to

reduce pain intensity or reduce depression over short, medium, or long-term. Adverse events were mild and more common in patients receiving TCAs than placebo (risk ratio (RR) 2.27; 95% CI 1.17-4.42) but did not result in more drug withdrawals. Rates of adverse events did not differ between amitriptyline and paroxetine and included central nervous system (22%) (somnolence, fatigue, headache and dizziness); anticholinergic (15%) (dry mouth, constipation and palpitations); and gastrointestinal (12%) (nausea and abdominal pain).

Assessment: No evidence supports the use of amitriptyline, imipramine, desipramine, trimipramine or dothiepin for treatment of rheumatoid arthritis pain or depression.

Fibromyalgia: A single Cochrane Review³⁰¹⁴³ evaluated the efficacy of amitriptyline in the treatment of fibromyalgia. Nine studies of 649 participants who received 25 mg to 50 mg of amitriptyline were included. Third-tier evidence found amitriptyline superior to placebo in producing a 50% reduction in pain relief (36% vs 11%, respectively; RR of 2.9; NNT 4.1). No differences were found for fatigue, poor sleep, quality of life or tender points. Treatment with amitriptyline resulted in more adverse events than placebo therapy (78% vs 48%, number needed to harm (NNT_H)=3.3). Evidence supporting the use of amitriptyline in fibromyalgia is weak. Although the evidence is not robust, it does not indicate that amitriptyline is ineffective and clinical practice supports its utility.

Assessment: Evidence supporting the use of amitriptyline in fibromyalgia is weak.

Neuropathic Pain: Four Cochrane reviews have evaluated the use of TCAs in neuropathic pain. One Cochrane Review¹⁴⁴ evaluated 6 trials of 310 patients which compared nortriptyline to other agents. Trials were of low to very low quality primarily due to small sample sizes and bias. Third-tier evidence found efficacy similar among all treatments, gabapentin, gabapentin plus nortriptyline, clomipramine, morphine, amitriptyline or placebo. Adverse events were more common with nortriptyline than placebo but not different than the other treatment groups. Thus, very low level evidence supports the efficacy of nortriptyline in the treatment of neuropathic pain.

The second Cochrane review¹⁴⁵ of 5 trials in 177 participants found the available evidence to be of low quality and fraught with methodological problems and bias. Desipramine performed better than placebo in individual studies. Very low-quality evidence did not find a difference in efficacy or tolerability between treatment with desipramine, fluoxetine, clomipramine or amitriptyline.

A third Cochrane Review¹⁴⁶ evaluated the use of imipramine for neuropathic pain. The evidence from 5 very low quality trials, including 168 participants, yielded only third-tier evidence. Comparator treatments included placebo, paroxetine, mianserin, venlafaxine or amitriptyline. Pooling of data was not possible. Overall, individual trials suggest imipramine may be efficacious in the treatment of neuropathic pain but associated with an increase in adverse events.

The fourth Cochrane Review¹⁴³ updated a previous review, that evaluated the efficacy and tolerability of amitriptyline in the treatment of neuropathic pain. Evidence from seventeen studies of 1492 participants found limited evidence of benefit. When data was pooled for trials of diabetic neuropathy, postherpetic neuropathy and mixed neuropathic pain (4 trials, 382

participants) amitriptyline was found superior to placebo, RR 2.0 (1.5 to 2.8) with a NNT of 5.1 (3.5 to 9.3). In the subset of participants treated for neuropathic pain associated with cancer or HIV, amitriptyline was ineffective. Participants reported developing at least one adverse event more commonly with amitriptyline than placebo (55% vs 36%) treatment. Similarly, the all-cause withdrawal rate was higher with amitriptyline (24% vs 18%). Overall, low-quality evidence suggests that TCAs are more efficacious than placebo and equivalent to other medications for use in the treatment of neuropathic pain not due to cancer or HIV.

Assessment: Low to very low quality evidence found no difference in safety or efficacy between amitriptyline, clomipramine, desipramine, nortriptyline which all performed better than placebo in the treatment of neuropathic pain not due to cancer or HIV.

Tension Headache: A Cochrane Review¹⁴⁷ evaluated the use of antidepressants in the treatment of tension headache. Included were 8 trials involving 412 participants. Interventions include SSRIs, SNRIs, amitriptyline, desipramine, sulpiride and mianserin. At 8-weeks, low to very low quality evidence did not find a difference between SSRIs, SNRIs and TCAs in reducing the frequency of tension headaches. Analgesic intake was reduced with TCA vs SSRIs (mean difference 4.98; 95% CI 1.12-8.84; I²= 0%). Adverse events occurred more commonly with TCA use, but no differences between groups were found for withdrawals from therapy overall or for withdrawals due to adverse events.

Assessment: Evidence does not support the use of TCAs in the treatment of tension headache.

Migraine Prophylaxis: A Cochrane Review¹⁴⁸ evaluated the use of antidepressants for migraine prevention. Included were 11 trials of 585 participants. Common to the studies were methodological and reporting shortcomings. The trials were of short duration, inadequately powered and often lacked results for migraine frequency, intensity or duration. In two trials that compared SSRIs/SNRIs to amitriptyline, no difference in migraine frequency was found between groups, (SMD 0.04 (95% CI, -0.72-0.80; I² = 72%). Tolerability was higher with SSRI/SNRI agents but withdrawal rates due to adverse events did not differ.

Assessment: Evidence is lacking to assess the efficacy of amitriptyline in migraine prophylaxis and no comparative TCA trials are available.

Attention Deficit Hyperactivity Disorder (ADHD): A Cochrane Review¹⁴⁹ evaluated the efficacy of antidepressants for the treatment of attention deficit hyperactivity disorder in children and adolescents. Included were 6 trials of 216 participants who received clomipramine, desipramine, nortriptyline, methylphenidate or clonidine. Desipramine improved the core symptoms of ADHD more than placebo assessed by parents, teachers and clinicians. Nortriptyline performed better than placebo by clinician assessment and better than clonidine on a number of ADHD scales with equivalent tolerability. Methylphenidate was more efficacious than desipramine and clomipramine with respect to ADHD symptom severity and behavior control scales, whereas clomipramine was more efficacious for depression measures. The TCAs produced statistically higher, but modest, diastolic blood pressure and pulse rate elevations compared to placebo. Although the agents do appear effective the cardiovascular effects may limit their utility in this setting. Applicability of the results is limited by the small size of the trials and differences in outcome assessment and reporting.

Assessment: Further evidence is needed to define the role of the TCAs in the treatment of ADHD. Methylphenidate appears more efficacious than TCAs which are associated with an undesirable side effect profile.

Autism Spectrum Disorder: A Cochrane Review¹⁵⁰ evaluated the use of TCAs (clomipramine and tianeptine) for autism spectrum disorder in children and adolescents. Three trials of small numbers could not be pooled. Two clomipramine trials yielded conflicting results. Improvements in autistic symptoms, irritability and obsessive compulsive symptoms were found with increased hyperactivity and no change in appropriate speech. Clomipramine use resulted in a higher dropout rate. Use should be limited until further positive evidence supports the benefit over risk for use of clomipramine or tianeptine.

Assessment: No evidence supports the use of TCAs in autism spectrum disorder.

Irritable Bowel Syndrome: A Cochrane Review¹⁵¹ compared pharmacotherapeutic options for the treatment of irritable bowel syndrome. From 56 trials of 3725 participants, 15 trials (N=922) evaluated the use of antidepressant therapies. A random effects model was used to evaluate the evidence, due to significant heterogeneity between trials. Compared to placebo therapy, SSRIs significantly improved global assessment scores (RR 1.79; 95% CI 1.01-3.20) whereas TCAs significantly improved abdominal pain (RR 1.26; 95% CI 1.03-1.55) and IBS symptom scores (RR 3.16; 95% CI 1.59-6.29).

Assessment: Placebo-controlled evidence demonstrates that TCAs may reduce abdominal pain and symptom scores in irritable bowel syndrome, however, medication specific subgroup analysis was not performed to differentiate between the TCAs.

Safety

Black Box Warnings⁴⁻⁶

All TCAs and TCA-combination products carry a Black Box warning for an increased risk of suicidal thinking and behavior in children, adults and young adults (18-24 years of age) with major depressive disorder and other psychiatric disorders. Evidence has found that the risk of suicide attempts or completed suicides is not different with any specific class of antidepressant in adults or children and adolescents.^{152,153}

Amitriptyline-perphenazine carries an additional Black Box warning concerning the increased risk of death in elderly patients with dementia-related psychosis treated with antipsychotic medications.

Contraindications⁴⁻⁶

All agents are contraindicated (CI) for hypersensitivity to the agent or class and for use within 14 days of discontinuing an MAOI (including linezolid or intravenous methylene blue). All agents, except doxepin, are contraindicated during the acute recovery phase following a myocardial infarction. Coadministration of amitriptyline or protriptyline with cisapride may prolong the QT interval and increase the risk of arrhythmia. CI specific to doxepin include glaucoma, including untreated narrow angle and urinary retention. CI specific to maprotiline include seizure disorders, seizure history or risk factors for seizures. CI to

amitriptyline/perphenazine include bone marrow depression and additive toxicity with concurrent CNS depressant use.

Warnings/Precautions⁴⁻⁶

TCAAs may cause a worsening of depression with suicide risk. Patients should be screened for bipolar disorder to prevent TCA-induced precipitation of a mixed/manic episode. Bipolar and hyperkinetic patients may develop hypomania. Due to risk of serious adverse reactions, these agents are not recommended as first-line therapy for depression. Amoxapine use has resulted in dose- and duration-related extrapyramidal side effects and the development of neuroleptic malignant syndrome. Clomipramine may cause hyperthermia. TCAs lower the seizure threshold increasing the risk of seizures in patients at risk. Mydriasis may precipitate narrow-angle glaucoma. Due to the TCAs anticholinergic effects, these agents should be prescribed cautiously in patients with reduced gastrointestinal motility, paralytic ileus, urinary retention, benign prostatic hyperplasia, xerostomia or visual abnormalities. Protriptyline use is associated with tachycardia and postural hypotension. TCAs should be used cautiously in patients with cardiovascular disorders including conduction defects. Patients at risk of hypotension are more likely to experience orthostatic changes. Use of TCAs has resulted in a worsening of psychosis, paranoid delusions, hostility, anxiety and agitation in psychiatric patients. Clomipramine use is most commonly associated with neuropsychiatric effects. Doxepin use increases the risk for hazardous sleep-related activities. TCAs, especially doxepin, should be used cautiously with respiratory compromise or sleep apnea. TCA-induced hypersensitivity rashes may be severe. TCAs increase the risks associated with electroconvulsive therapy. When possible, discontinue TCAs prior to elective surgery, but not abruptly. TCAs alter glucose control in diabetic patients. Bone fracture risk is increased with TCA use. Male sexual function is adversely affected by clomipramine which may also cause weight gain. Bone marrow suppression may occur with any of the agents. A discontinuation syndrome has occurred sometimes with psychological symptoms. It is more common with shorter half-life TCAs, longer durations of therapy or abrupt withdrawal. Doxepin should be used for sleep only after assessing the cause of the insomnia. Use TCAs with caution in renal impairment. Hepatic dysfunction may require lower dosages to prevent accumulation. Clomipramine is associated with potentially fatal hepatotoxicity; periodic hepatic enzyme monitoring is recommended in patients with baseline disease or risk. TCAs may increase the risks associated with performing hazardous tasks. Imipramine may cause photosensitivity. TCAs must be used with caution in children and the elderly (see Special Populations section for further information).

Adverse Effects

Many of the adverse effects of TCA therapy relate to pharmacological activity. The use of TCAs are often limited by anticholinergic and antihistaminic side effects.¹⁵⁴ TCAs may cause delirium, delayed cardiac conduction, orthostatic hypotension, photosensitivity and the development of glaucoma.¹ A narrow therapeutic range can produce cardiotoxicity and seizures at doses less than 10 times the daily recommended dose.¹¹⁶ See **Table 13** for a comparison of the agents.

Table 13: Pharmacologic Activity and Adverse Event Profile of TCAs ^{6,127,155}

Medication	NE Activity	5HT Activity	H1 Activity	Anticholinergic	Seizures	Weight Gain	Cardiac	Sedation	Orthostatic Hypotension
Tertiary Amines									
Amitriptyline	2+	4+	3+	3+	2+	2+	3+	3+	3+
Clomipramine	2+	5+	2+	3+	3+	2+	3+	2+	2+
Doxepin	1+	2+	3+	2+	2+	2+	3+	3+	2+
Imipramine	2+	4+	2+	2+	2+	2+	3+	2+	2+
Trimipramine	1+	1+	2+	3+	2+	2+	3+	3+	2+
Secondary Amines									
Amoxapine	3+	2+	2+	1+	2+	1+	2+	1+	2+
Desipramine	4+	2+	2+	1+	1+	1+	2+	0/1+	1+
Nortriptyline	2+	3+	1+	1+	1+	1+	2+	1+	1+
Protriptyline	4+	2+	0/1+	2+	2+	1+	3+	0/1+	1+
Tetracyclic Amines									
Maprotiline	3+	0/1+	2+	2+	3+		2+	2+	1+

Cardiac Disease: A review by Alvarez Jr. et al¹⁵⁶ evaluated the literature concerning the safety of antidepressant drugs in patients with cardiac disease. Orthostatic hypotension is a common adverse event with tricyclic antidepressant therapy. Tricyclic tertiary amines (e.g. amitriptyline) cause more significant orthostatic effects than secondary amines (e.g. nortriptyline), which are preferred in patients at risk. Risk factors include preexisting postural hypotension or concomitant use of other antihypertensive medications. Tricyclics should be used cautiously in patients at risk.¹⁵⁶ This review found that the use of imipramine or doxepin was acceptable in patients without left ventricular dysfunction or coronary artery disease. Further, in patients with an ejection fraction below 40%, short term use of imipramine produced significant orthostatic hypotension although both imipramine and nortriptyline appeared to be safe. Short-term evidence supports the safety of TCAs in patients with ischemic heart disease, heart failure or prior myocardial infarction. TCAs reduce the frequency of PVCs but evidence has not defined the safety of these agents in patients with cardiac conduction disturbances. Evidence is lacking to define the long-term safety TCAs and it is unlikely that studies designed to answer these safety questions will be performed.

Central Nervous System:¹ Confusion and delirium occur with TCAs in a concentration-dependent manner. Patients with psychotic depression and dementia are at increased risk. These patients should be treated with TCAs having less anticholinergic activity (e.g. secondary amine TCAs). The development of seizures on TCA therapy believed to be a result of chloride conductance changes mediated by the inhibition of the γ -aminobutyric acid (GABA) receptor chloride-ionophore complex. The development of seizures is both dose and concentration-dependent. Tremors occur in a dose-dependent manner and may be a marker for TCA toxicity. Amoxapine is metabolized to 7-hydroxy amoxapine which has significant neuroleptic properties. Rarely, amoxapine use has resulted in the development of neuroleptic malignant syndrome or tardive dyskinesia.

Tolerability: A retrospective, database analysis of 75 managed care plans (covering 55 million persons) assessed antidepressant tolerability.¹⁵⁷ A change in therapy occurred more often with TCA or MAOIs (40.1%) than with SSRIs/SNRI (21.2%) or newer antidepressants (18.3%). Adherence rates demonstrated a similar trend (12.4% vs 29.3% vs 33.6%, respectively).

Treatment with TCA/MAOIs for 6 months was associated with significantly higher odds for all-cause hospitalizations and costs.

Bone Fracture: A meta-analysis by Gagne et al¹⁵⁸ compared the risk of fracture in older adults receiving antidepressants. They reviewed Medicare databases in two states and identified 73,072 older adults using antidepressants. They used Cox proportional hazards models to compare fracture rates (hip, humerus, pelvis, waist and composite) against propensity score-matched cohorts of participants receiving tricyclic secondary amines (N=2916), tricyclic tertiary amines (N=4,701), SSRIs, (N=56,941) or atypical antidepressants (N=8,514). Composite fracture rates were highest with SSRI use (46.6 per 1,000 person-years; 95% CI 42.0–51.6), atypical antidepressants (39.9 per 1,000 person-years; 95% CI 35.6–44.6) and lowest with both secondary amine tricyclics (34.4 per 1,000 person-years; 95% CI 30.7–38.5) and tertiary amine tricyclics (34.5 per 1,000 person-years; 95% CI 30.8–38.5). Users of SSRIs had a 30% greater likelihood of fracture than those receiving tricyclic secondary amines corresponding to an incidence rate difference of 12 events per 1000 exposed person years.

Venous Thromboembolism: Jick et al¹⁵⁹ performed a nested-case control study of antidepressant-treated patients who developed a venous thromboembolism (VTE). Case patients were defined as patients who developed an idiopathic VTE while receive antidepressant therapy. Four control patients were matched to each case patient (N=782). The risk of a VTE was increased only with use of tricyclic antidepressants. Of the TCAs, only amitriptyline was found significantly associated with increased VTE risk (OR 1.7, 95% CI 1.2-2.4). The risk was increased in patients receiving ≥ 25 mg amitriptyline per day. Additionally, the risk was higher in patients receiving amitriptyline for a psychiatric indication as opposed to pain, neuralgia or undetermined use. Of note, the study did not report the number of patients receiving different antidepressants and did mention that the subset of patients receiving amitriptyline was small.

Toxicity

TCA toxicity develops rapidly after overdose.^{4-6,160} Significant cardiac dysrhythmias, hypotension, convulsions, CNS depression and coma are common. EKG changes include rightward axis shift of the QRS complex, QT prolongation, prolonged PR interval, ST-T changes, sinus tachycardia ventricular tachycardia or fibrillation may occur. Children are more sensitive to TCAs and overdose is often fatal. Other factors predictive of toxicity include age, amount ingested and the time between ingestion and treatment. CNS and respiratory depression are common. Amoxapine presents differently with tonic-clonic seizures or status epilepticus, coma and acidosis. A small portion of patients with amoxapine overdose develop renal failure with acute tubular necrosis, rhabdomyolysis and myoglobinuria.

Drug Interactions

Some of the most common mechanisms by which tricyclic antidepressants produce drug interactions include additive effects with other serotonergic medications, CYP450 enzyme interactions, anticholinergic cardiac and cardiovascular effects.^{1,2,4-6,127,161,162} **Table 14** lists TCA drug interactions.

Serotonin Syndrome: Serotonin syndrome is a potentially fatal syndrome.^{118,127} In combination with other serotonergic medications, TCA potency is positively correlated with the development of serotonin syndrome.^{118,127} Imipramine and less potent agents are unlikely to

produce a reaction, while clomipramine a very potent TCA is much more likely to be involved in a reaction. Likewise, amphetamine and linezolid is a strong releaser while methylphenidate exerts weak activity. Known fatalities presented in order of frequency have been reported with SSRIs, clomipramine, imipramine, venlafaxine, tramadol, meperidine and possibly fentanyl.^{118,127,163}

CYP450 Hepatic Enzyme Mediated Interactions:⁴⁻⁶ Tricyclic antidepressants interact with CYP450 enzymes, however, the interactions are of less significance than with SSRI antidepressants.¹²⁷ Preskorn and Flockhart¹⁶⁴ suggest that the FDA would not likely approve fluoxetine and fluvoxamine today due to the significant interactions. Desipramine and nortriptyline are weak CYP2D6 inhibitors and involved in significant interactions only at high serum concentrations. CYP2C19 and CYP1A2 substrate metabolism are inhibited by the tertiary amines (amitriptyline, imipramine, clomipramine), although doxepin interactions are uncommon at sedative doses. Use of immune suppressants (e.g. peg interferon) with TCAs metabolized by 2D6 may result in increased TCA concentrations. Bupropion via CYP2D6 inhibition increases TCA and bupropion concentrations and increases the risk of seizures. Concentrations of anthracycline antineoplastics may be increased by CYP2D6 inhibition.

Cardiac Conduction: TCAs exert quinidine-like effects on the heart.^{162,165} Combination therapy with other medications affecting cardiac conduction places patients at significant risk for cardiotoxicity. Medications which may interact and should be avoided in patients receiving TCA therapy include, alfuzosin, antiarrhythmics, antipsychotics, apomorphine, cisapride, fluoroquinolone antibiotics, antimalarials, macrolide antibiotics, antiretrovirals (e.g. saquinavir), BRAF (B-raf kinase) inhibitors (e.g. dabrafenib), chloral hydrate, chlorpromazine, cotrimoxazole, dextromethorphan, eliglustat, fingolimod, donepezil, droperidol, foscarnet, general anesthetics, gonadotropin releasing hormone agonists (e.g. gonadorelin), hydroxychloroquine, imidazole antifungals, isradipine, ivabradine, methadone, metronidazole, other TCAs, panobinostat, pasireotide, phenothiazines, quinine, solifenacin, sorafenib, sunitinib, tacrolimus, telavancin, tetrabenazine, toremifene, tramadol, trazodone tyramine kinase inhibitors (e.g. nilotinib) and vardenafil. Patients are additionally at risk if they have underlying cardiopathy, defects in cardiac conduction, rhythm, or electrolyte disturbances.

Table 14: Drug Interactions with TCA Antidepressants

Mediation Class/Specific Agent	Interaction Effect
Other Antidepressants	
Additive TCA/Tetracyclics	Abnormal heart rhythm
SSRIs/SNRIs	Levels of TCA, SSRI , SNRI may increase Abnormal heart rhythms
MAOIs including methylene blue and linezolid	Serotonin syndrome (esp. with clomipramine), hypotension and hypertensive reactions, neurotoxicity, seizures
Serotonin antagonists	Hypotension
Bupropion	Increased seizure risk (significant)
Antibiotics/Antifungals/HIV	
Chloramphenicol, isoniazid, imidazoles (fluconazole, itraconazole, ketoconazole, miconazole)	Increased TCA levels and risk of TCA toxicity
Doxycycline, Griseofulvin	Reduced TCA levels and effectiveness
Antiretrovirals (e.g saquinavir)	Increased TCA concentrations
Diabetic Agents	

Mediation Class/Specific Agent	Interaction Effect
Insulin, oral hypoglycemic agents	Enhanced hypoglycemic response
Other Medical Conditions	
Glaucoma	May trigger narrow-angle glaucoma attack
Heart disease	Abnormal heart rhythms, long QT syndrome
Liver disease	Hepatic metabolism may be reduced resulting in higher levels and toxicity
Seizure disorder	Risk of seizures from lowered seizure threshold
Thyroid disease	Abnormal heart rhythms
High-fiber diet	Reduced absorption of TCA
Cardiovascular Medications	
Disopyramide	Abnormal heart rhythms
Sympathomimetics (e.g. epinephrine)	Increased epinephrine effects, including tachycardia, hypertension and abnormal heart rhythms
Quinidine	Increased levels of both quinidine and TCA producing abnormal heart rhythms, heart muscle weakness and possibly congestive heart failure
Beta-blockers	Hypotension and aggravated depression
Clonidine	Reduced clonidine effectiveness
Calcium channel blockers	Enhanced hypotensive response
Acetazolamide	Enhanced hypotensive response
Guanethidine	Diminished antihypertensive effect
Methyldopa	Amitriptyline enhances hypotension Desipramine diminishes antihypertensive effect
Prazosin	Diminished antihypertensive response
Reserpine, thiazide diuretics	Enhanced hypotensive response
Anticonvulsants – Mood Stabilizers	
Carbamazepine (CBZ)	Reduced TCA and CBZ levels, increased potential for seizures
Isocarboxazid	Increased risk of neurotoxicity, seizures and serotonin syndrome
Lithium(Enhanced antidepressant effects
Phenytoin	Increased potential for seizures
Valproate (VPA)	Increased levels of TCA and VPA with potential for toxicity
Pain Medications - Anesthetics	
Acetaminophen (ACTM)	Increased TCA levels, decreased ACTM levels
Aspirin	Increased TCA levels
Halothane	Increased TCA levels, arrhythmogenic**
Cyclobenzaprine	Arrhythmogenic
Methadone	Methadone levels increase significantly*
Opioids	Enhanced narcotic effects (use lower doses), paralytic ileus, CNS and respiratory depression
NSAIDs	Increased risk of bleeding
Pancuronium	Arrhythmogenic**
Sedatives - Tranquilizers	
Alcohol, barbiturates, buspirone, chloral hydrate	Enhanced sedation; reduced TCA levels
Phenothiazine neuroleptics	Increased neuroleptic and TCA levels; enhanced arrhythmogenic potential with thioridazine, clozapine, pimozide
Minor tranquilizers (neuroleptics)	Enhanced sedation
Stimulants	

Mediation Class/Specific Agent	Interaction Effect
Amphetamines, cocaine, methylphenidate	Elevated levels of imipramine, clomipramine, desipramine, hypertension, arrhythmogenic
Other Medications	
Albuterol, levalbuterol	Increased cardiovascular toxicity (e.g. tachycardia, blood pressure changes)
Anticholinergics	Increase anticholinergic effects
Antihistamines	Enhanced drowsiness; second-generation antihistamines are preferred
Estrogen-containing medications	Lower doses increase TCA levels and adverse effects while higher doses decrease TCA effects
Alkylating antineoplastics (e.g. procarbazine)	Increased neurotoxicity, seizures
Caffeine, cimetidine, disulfiram‡, prochloroperazine, scopolamine, theophylline	TCA levels may increase
Cholestyramine, psyllium, levodopa	TCA levels may decrease
Ephedrine	Reduced ephedrine levels and effects
Immune suppressants (e.g. peg interferon)	
Levothyroxine	Increased levels of levothyroxine and TCA
Liothyronine	TCA levels may increase, arrhythmogenic effects
Metoclopramide	Increased risk of extrapyramidal reactions and neuroleptic malignant syndrome

Key: TCA-tricyclic antidepressant; SSRI-selective serotonin reuptake inhibitor; SNRI-serotonin-norepinephrine reuptake inhibitor; *-most notable with desipramine; ** - most notable with anticholinergic TCAs; †-Organic brain syndrome occurred with amitriptyline; ACTM-acetaminophen; CBZ-carbamazepine; VPA-valproic acid

Summary:

Evidence supporting the use of tricyclic antidepressants is limited with issues of bias, power, robustness and heterogeneity in measuring instruments and populations. Additionally, methodological and reporting shortcomings were common. Migraine prophylaxis trials were of too short of duration. In general, data was not assessed to the level of the individual medication. The majority of evidence is categorized as low to very low quality according to Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) guidelines^{166,167} and further studies are needed to confirm the place of TCAs in therapy. Pooled together, the evidence suggests the following:

The majority of evidence is categorized as low to very low quality and further studies are needed to confirm the place of TCAs in therapy. Pooled together, the evidence suggests the following:

Depression: Efficacy was not different between individual TCAs or fluoxetine in the treatment of major depressive disorder, although fluoxetine was better tolerated than amitriptyline, clomipramine and imipramine. Grouped TCAs (desipramine, imipramine and nortriptyline) appeared to perform as well as SSRIs in the physically-ill depressed with an earlier response to treatment, but analysis to the level of the individual TCA could not be performed. Amitriptyline performed statistically superior, although not likely clinically superior, to grouped comparators (SSRIs, tricyclic and tetracyclic antidepressants) in the treatment of depression, although amitriptyline therapy was associated with more adverse events and lower tolerability. Grouped TCAs (amitriptyline, clomipramine, desipramine, dothiepin, doxepin, imipramine, nortriptyline) were as efficacious as SSRIs or atypical antidepressants in treating the depressed elderly. No differences in efficacy or tolerability were noted between SSRIs and TCA therapy. TCAs were found potentially more efficacious in preventing recurrence during depression-maintenance-

therapy in the elderly. Low-dose TCA therapy (<100 mg daily of amitriptyline, clomipramine, desipramine, doxepin and trimipramine) was as effective as standard dose therapy for the treatment of depression and associated with fewer adverse events. Evidence does not support the use of TCAs in the treatment of depressed adults with cancer or children or adolescents with depression or anxiety disorders.

Pain: Amitriptyline use to reduce fibromyalgia pain is supported by weak evidence. In the treatment of non-cancer/non-HIV neuropathic pain, low to very-low quality evidence supports amitriptyline, clomipramine, desipramine and nortriptyline as equally efficacious. Evidence does not support the use of amitriptyline, imipramine, desipramine, trimipramine or dothiepin for use in rheumatoid arthritis pain. Additionally, the use of TCA therapy was ineffective to improve depressive symptoms in depressed rheumatoid arthritis patients with pain.

Irritable Bowel Syndrome: Evidence found the TCAs efficacious in reducing symptom scores and abdominal pain but individual medication comparative evidence remains lacking.

ADHD: In the treatment of ADHD, desipramine and nortriptyline demonstrated improvement in core symptoms which was not superior to methylphenidate. Cardiovascular side effects limit the utility of TCAs, pending the availability of further evidence.

Insufficient Evidence: Insufficient Evidence exists to support a role for desipramine or imipramine in the treatment of nocturnal enuresis; for amitriptyline or desipramine in treatment of tension headache; for amitriptyline in migraine prophylaxis or for clomipramine in autism spectrum disorder.

Safety:

Many of the adverse effects of TCA therapy relate to pharmacological activity. TCAs may cause confusion, delirium, delayed cardiac conduction, orthostatic hypotension, seizures, photosensitivity and the development of glaucoma. A narrow therapeutic range can produce cardiotoxicity and seizures at doses less than 10 times the daily recommended dose. TCAs should be used cautiously in the elderly who are more sensitive to anticholinergic side effects and orthostatic hypotension. Dosing TCAs should include consideration of genetic variation on hepatic microsomal metabolism. TCAs should be avoided or used with caution in patients with underlying cardiovascular disease or conduction defects. MAOIs may increase the risk of suicidality in young people and may activate mania/hypomania in patients with undiagnosed bipolar disorder. TCAs, especially clomipramine, may worsen psychosis, delusions and agitation in psychiatric patients. TCAs increase hypoglycemia in diabetes and may increase bone fracture risk. TCAs may cause bone marrow suppression, sexual dysfunction, weight gain and abrupt discontinuation may cause a withdrawal reaction. Hepatotoxicity may occur with clomipramine. Amoxapine use is associated with neuroleptic malignant syndrome and tardive dyskinesia. TCAs, particularly amitriptyline, may increase the risk of venous thromboembolism. TCAs are toxic in overdose, with children more at risk, and patients should be carefully screened for risk of suicidality prior to initiating therapy.

Some of the most common mechanisms by which tricyclic antidepressants produce drug interactions include additive effects with other serotonergic medications, CYP450 enzyme interactions, anticholinergic cardiac and cardiovascular effects. Potentially fatal serotonin syndrome may occur with TCAs in combination with MAOIs or serotonin reuptake inhibitors

including SSRIs, SNRIs as well as with the weak inhibitors, meperidine, fentanyl and tramadol. TCAs should not be used within 14 days of discontinuing MAOI therapy. TCAs interact with hepatic microsomal metabolism of other medications and substrates, although the effect is less significant than with SSRIs/SNRIs.

Summary:

Clinical practice guidelines consider TCAs effective, first-line therapy for the treatment of depression, but use remains low as safer alternatives are available. Guidelines consider TCAs alternatives to first- and second-line therapies for other indications.

The strength of the evidence supporting the use of tricyclic antidepressants is limited by issues of bias, power, robustness and significant heterogeneity in both measuring instruments and populations. Additionally, methodological and reporting shortcomings were common, for instance, migraine prophylaxis trials were conducted for too short a duration. Comparative trials were rare and pooled evidence was not assessed to the level of the individual TCA medications. Finally, the majority of evidence is categorized as low to very low in quality and further studies are needed to confirm the place of TCAs in therapy.

Evidence suggests amitriptyline is as efficacious as SSRIs in the treatment of depression although associated with a higher adverse event rate and lower tolerability than either SSRIs or other TCAs. Amitriptyline appears to be efficacious in the treatment of fibromyalgia. In the treatment of neuropathic pain, amitriptyline, clomipramine, desipramine and nortriptyline were found equally efficacious.

Evidence suggests but is insufficient to prove that TCAs produce a more rapid response in depression than SSRIs; that low-dose TCA therapy is as efficacious as standard dose therapy with less adverse events in the treatment of depression; that TCAs are as effective as other therapies in the depressed elderly and may prevent depressive recurrence better than other classes of antidepressants; that TCAs have a role in the treatment of ADHD despite their cardiac event profile and that TCAs reduce pain and symptom scores in inflammatory bowel disease.

TCAs appear to be ineffective in the treatment of depressed adults with cancer or HIV, in children with depression or anxiety disorders, in autism spectrum disorder, nocturnal enuresis, treatment of tension headache, migraine prophylaxis and rheumatoid arthritis pain.

Many of the adverse effects of TCA therapy relate to pharmacological activity. The elderly are more sensitive to anticholinergic side effects including orthostatic hypotension. TCAs should be used cautiously in the presence of cardiovascular disease, conduction defects, patients at risk of suicide, with bipolar illness, in patients receiving hypoglycemic therapy. TCAs may increase bone fracture risk and the development of venous thromboembolism. TCAs may cause bone marrow suppression, sexual dysfunction, weight gain and abrupt discontinuation may cause a withdrawal reaction. Hepatotoxicity may occur with clomipramine. Amoxapine use is associated with neuroleptic malignant syndrome and tardive dyskinesia.

Some of the most common mechanisms by which tricyclic antidepressants produce drug interactions include additive effects with other serotonergic medications, CYP450 enzyme interactions and anticholinergic mediated cardiac and cardiovascular effects. Potentially fatal serotonin syndrome may occur with TCAs in combination with MAOIs or serotonin reuptake inhibitors including SSRIs, SNRIs as well as with the weak serotonin inhibitors, meperidine,

fentanyl and tramadol. TCAs should not be used within 14 days of discontinuing MAOI therapy. TCAs interact with hepatic microsomal metabolism of other medications and substrates, although the effect is less significant than with SSRIs/SNRIs.

Evidence is insufficient to establish differences between TCAs. Selection of TCA therapy should consider current clinical practice guidelines, patient comorbidities, concomitant and recently discontinued medications, use of- and response to prior therapies, the adverse effect/drug interaction/pharmacologic activity profile of the particular TCA and patient and prescriber preferences.

References

1. Nelson JC. Tricyclic and Tetracyclic Drugs. *The American Psychiatric Publishing Textbook of Psychopharmacology*: American Psychiatric Publishing; 2009.
2. O'Donnell JM, Shelton RC. Drug Therapy of Depression and Anxiety Disorders. In: Brunton LL, Chabner BA, Knollmann BC, eds. *Goodman & Gilman's: The Pharmacological Basis of Therapeutic*. 12th ed. New York, NY: McGraw-Hill; 2011.
3. Hirsch M BR. Tricyclic and Tetracyclic Drugs: Pharmacology, administration and side effects. *UpToDate*. 2016. <http://www.uptodate.com/contents/tricyclic-and-tetracyclic-drugs-pharmacology-administration-and-side-effects>.
4. Facts & Comparisons. Wolters Kluwer; 2016. <http://www.wolterskluwercdi.com/facts-comparisons-online/>.
5. Micromedex. Truven Health Analytics, Inc.; 2016. <http://www.micromedexsolutions.com/micromedex2/librarian>.
6. Lexi-Drugs. Wolters Kluwer; 2015. http://online.lexi.com/lco/action/index/dataset/patch_f. Accessed 11/7/15.
7. <http://www.nimh.nih.gov/health/statistics/prevalence/any-mood-disorder-among-adults.shtml> NMDS.
8. <http://www.adaa.org/about-adaa/press-room/facts-statistics>. AFaS.
9. CDC. Mental Health Basics. 2016; <http://www.cdc.gov/mentalhealth/basics/burden.htm>.
10. <http://www.cdc.gov/mentalhealth/basics/burden.htm>. CMHB.
11. CDC. Databriefs. 2016; <http://www.cdc.gov/nchs/data/databriefs/db135.ht#x2013;2010>.
12. McDonagh M, Peterson K, Carson S, Fu R, Thakurta S. Drug Class Reviews. *Drug Class Review: Atypical Antipsychotic Drugs: Final Update 3 Report*. Portland (OR): Oregon Health & Science University Portland, Oregon 97239. All rights reserved.; 2010.
13. Reus VI. Mental Disorders. In: Kasper D, Fauci A, Hauser S, Longo D, Jameson JL, Loscalzo J, eds. *Harrison's Principles of Internal Medicine, 19e*. New York, NY: McGraw-Hill Education; 2015.
14. SAMHSA.gov. Behavioral Health Barometer: Utah hwsghdsdfSBB-Up.
15. Singh T, Williams K. Atypical Depression. *Psychiatry (Edgmont)*. 2006;3(4):33-39.
16. PhRMA. The Pharmaceutical Industry: An Industry Note 2008. http://www.wiley.com/legacy/wileychi/ginter/supp/Case_1.pdf.
17. Thase ME. When are psychotherapy and pharmacotherapy combinations the treatment of choice for major depressive disorder? *The Psychiatric quarterly*. 1999;70(4):333-346.
18. Dupuy JM, Ostacher MJ, Huffman J, Perlis RH, Nierenberg AA. A critical review of pharmacotherapy for major depressive disorder. *The international journal of neuropsychopharmacology / official scientific journal of the Collegium Internationale Neuropsychopharmacologicum (CINP)*. 2011;14(10):1417-1431.
19. Sansone RA, Sansone LA. Antidepressant Adherence: Are Patients Taking Their Medications? *Innovations in Clinical Neuroscience*. 2012;9(5-6):41-46.
20. Preskorn SH. Outpatient Management of Depression. 2010; http://www.preskorn.com/books/omd_s7.html. Accessed 8/30, 2016.
21. Bauer M, Whybrow PC, Angst J, et al. World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for biological treatment of unipolar depressive disorders,

- part 1: Acute and continuation treatment of major depressive disorder. *Revista de Psiquiatria Clinica*. 2009;36(SUPPL. 2):17-57.
22. Bauer M, Severus E, Kohler S, Whybrow PC, Angst J, Moller HJ. World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for biological treatment of unipolar depressive disorders. part 2: maintenance treatment of major depressive disorder-update 2015. *The world journal of biological psychiatry : the official journal of the World Federation of Societies of Biological Psychiatry*. 2015;16(2):76-95.
 23. NICE. Depression in adults: recognition and management (CG90). 2009; <https://www.nice.org.uk/Guidance/CG90>.
 24. National Collaborating Centre for Mental H. National Institute for Health and Clinical Excellence: Guidance. *Depression: The Treatment and Management of Depression in Adults (Updated Edition)*. Leicester (UK): British Psychological Society Copyright (c) The British Psychological Society & The Royal College of Psychiatrists, 2010.; 2010.
 25. Association AP. Practice Guideline for the Treatment of Patients with Major depressive disorder. . 2010.
 26. Trangle M GJ, Haight R, Hardwig J, Hinnenkamp T, Kessler D, Mack N, Myszkowski M. Adult Depression in Primary Care. . 2016. https://www.icsi.org/_asset/fnhdm3/depr-interactive0512.pdf.
 27. Kennedy SH, Lam RW, McIntyre RS, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 Clinical Guidelines for the Management of Adults with Major Depressive Disorder: Section 3. Pharmacological Treatments. *Canadian journal of psychiatry. Revue canadienne de psychiatrie*. 2016;61(9):540-560.
 28. Birmaher B, Brent D. Practice Parameter for the Assessment and Treatment of Children and Adolescents With Depressive Disorders. *Journal of the American Academy of Child & Adolescent Psychiatry*.46(11):1503-1526.
 29. DeBattista C. Antidepressant Agents. In: Katzung BG, Trevor AJ, eds. *Basic & Clinical Pharmacology*. 13th ed. New York, NY: McGraw-Hill; 2015.
 30. Sinyor M, Schaffer A, Levitt A. The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial: A review. *Canadian Journal of Psychiatry*. 2010;55(3):126-135.
 31. Schmitt R, Gazalle FK, Lima MS, Cunha A, Souza J, Kapczinski F. The efficacy of antidepressants for generalized anxiety disorder: a systematic review and meta-analysis. *Revista brasileira de psiquiatria (Sao Paulo, Brazil : 1999)*. 2005;27(1):18-24.
 32. NICE. Social anxiety disorder: recognition, assessment and treatment (CG159). 2013. <https://www.nice.org.uk/guidance/cg159/>.
 33. Kessler RC, Petukhova M, Sampson NA, Zaslavsky AM, Wittchen HU. Twelve-month and lifetime prevalence and lifetime morbid risk of anxiety and mood disorders in the United States. *International journal of methods in psychiatric research*. 2012;21(3):169-184.
 34. Stein DJ, Ipser JC, van Balkom AJ. Pharmacotherapy for social anxiety disorder. *Cochrane Database of Systematic Reviews*. 2000(4).
 35. Ipser JC, Stein DJ, Hawkrigde S, Hoppe L. Pharmacotherapy for anxiety disorders in children and adolescents. *Cochrane Database of Systematic Reviews*. 2009(3).
 36. Ipser JC, Wilson D, Akindipe TO, Sager C, Stein DJ. Pharmacotherapy for anxiety and comorbid alcohol use disorders. *The Cochrane database of systematic reviews*. 2015;1:Cd007505.

37. School of H, Related Research UoS. National Institute for Health and Clinical Excellence: Guidance. *Clinical Guidelines for the Management of Anxiety: Management of Anxiety (Panic Disorder, with or without Agoraphobia, and Generalised Anxiety Disorder) in Adults in Primary, Secondary and Community Care*. London: National Collaborating Centre for Primary Care (UK) National Collaborating Centre for Primary Care.; 2004.
38. NICE. Generalised anxiety disorder and panic disorder in adults: management (CG113). 2011. <https://www.nice.org.uk/Guidance/CG113>.
39. Ropper AH, Samuels MA, Klein JP. Chapter 24. Fatigue, Asthenia, Anxiety, and Depression. *Adams and Victor's Principles of Neurology, 10e*. New York, NY: The McGraw-Hill Companies; 2014.
40. Mental Disorders. 2015; <http://samhsa.gov/disorders/mental>. Accessed 8/15, 2016.
41. Sadock BJ SV. Kaplan & Sadock's Synopsis of Psychiatry. In: Murphy J, ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2007: <https://books.google.com/books?hl=en&lr=&id=fFi7DR2hmaIC&oi=fnd&pg=PA7&dq=sadock+bj+lippincott+2007+obsessive&ots=bVnBYnD2U9&sig=sgY4VlcRA1nl-gI6ny9EqXWZNEI#v=onepage&q&f=true>.
42. Obsessive-Compulsive Disorder. 2016; <http://www.nimh.nih.gov/health/topics/obsessive-compulsive-disorder-ocd/index.shtml>. Accessed 8/6, 2016.
43. Mathis MA, Alvarenga P, Funaro G, et al. Gender differences in obsessive-compulsive disorder: a literature review. *Revista brasileira de psiquiatria (Sao Paulo, Brazil : 1999)*. 2011;33(4):390-399.
44. Soomro GM. Obsessive compulsive disorder. *BMJ clinical evidence*. 2012;2012.
45. Practice parameter for the assessment and treatment of children and adolescents with obsessive-compulsive disorder. *Journal of the American Academy of Child and Adolescent Psychiatry*. 2012;51(1):98-113.
46. Campbell M, Cueva JE. Psychopharmacology in child and adolescent psychiatry: a review of the past seven years. Part II. *Journal of the American Academy of Child and Adolescent Psychiatry*. 1995;34(10):1262-1272.
47. Hewlett WA. Chapter 21. Obsessive-Compulsive Disorder. In: Ebert MH, Loosen PT, Nurcombe B, Leckman JF, eds. *CURRENT Diagnosis & Treatment: Psychiatry, 2e*. New York, NY: The McGraw-Hill Companies; 2008.
48. Bandelow B, Zohar J, Hollander E, et al. World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the pharmacological treatment of anxiety, obsessive-compulsive and post-traumatic stress disorders - first revision. *The world journal of biological psychiatry : the official journal of the World Federation of Societies of Biological Psychiatry*. 2008;9(4):248-312.
49. Geller DA, March J. Practice Parameter for the Assessment and Treatment of Children and Adolescents With Obsessive-Compulsive Disorder. *Journal of the American Academy of Child & Adolescent Psychiatry*. 51(1):98-113.
50. Koran LM, Hanna GL, Hollander E, Nestadt G, Simpson HB. Practice guideline for the treatment of patients with obsessive-compulsive disorder. *The American journal of psychiatry*. 2007;164(7 Suppl):5-53.
51. Obsessive-Compulsive Disorder and Body Dysmorphic Disorder (CG31). 2005. <https://www.nice.org.uk/guidance/cg31/chapter/1-guidance>.

52. Ursano RJ, Bell C, Eth S, et al. Practice guideline for the treatment of patients with acute stress disorder and posttraumatic stress disorder. *The American journal of psychiatry*. 2004;161(11 Suppl):3-31.
53. Hetrick SE, Purcell R, Garner B, Parslow R. Combined pharmacotherapy and psychological therapies for post traumatic stress disorder (PTSD). *The Cochrane database of systematic reviews*. 2010(7):Cd007316.
54. Amos T, Stein DJ, Ipser JC. Pharmacological interventions for preventing post-traumatic stress disorder (PTSD). *Cochrane Database of Systematic Reviews*. 2014(7).
55. PTSD Statistics. 2013; <http://www.ptsdunited.org/ptsd-statistics-2/>.
56. Kessler RC, Sonnega A, Bromet E, Hughes M, Nelson CB. Posttraumatic stress disorder in the National Comorbidity Survey. *Archives of general psychiatry*. 1995;52(12):1048-1060.
57. Disorder. AGftToASDaPS. <http://phoenixaustralia.org/wp-content/uploads/2015/03/Phoenix-ASD-PTSD-Guidelines.pdf>.
58. Group TMoP-TSW. VA/DoD Clinical Practice Guideline for Management of Post-Traumatic Stress. 2010. <http://www.healthquality.va.gov/guidelines/MH/ptsd/cpgPTSDFULL201011612c.pdf>.
59. National Guideline C. Clinical guideline for the treatment of primary insomnia in middle-aged and older adults. 2014.
60. Morgenthaler T, Kramer M, Alessi C, et al. Practice parameters for the psychological and behavioral treatment of insomnia: an update. An american academy of sleep medicine report. *Sleep*. 2006;29(11):1415-1419.
61. Schutte-Rodin S, Broch L, Buysse D, Dorsey C, Sateia M. Clinical guideline for the evaluation and management of chronic insomnia in adults. *Journal of clinical sleep medicine : JCSM : official publication of the American Academy of Sleep Medicine*. 2008;4(5):487-504.
62. Stoller MK. Economic effects of insomnia. *Clinical therapeutics*. 1994;16(5):873-897; discussion 854.
63. Bonnett MH AD. Treatment of Insomnia. In: AF E, ed. *UpToDate*: WoltersKluwer; 2016.
64. Qaseem A, Kansagara D, Forcica MA, Cooke M, Denberg TD. Management of Chronic Insomnia Disorder in Adults: A Clinical Practice Guideline From the American College of Physicians. *Annals of internal medicine*. 2016;165(2):125-133.
65. CDC. Bipolar Mental Health Basics. 2016; <http://www.cdc.gov/mentalhealth/basics/mental-illness/bipolar.htm>. Accessed 7/25, 2016.
66. Merikangas KR, Jin R, He JP, et al. Prevalence and correlates of bipolar spectrum disorder in the world mental health survey initiative. *Archives of general psychiatry*. 2011;68(3):241-251.
67. Safer DJ, Zito JM, Safer AM. Age-grouped differences in bipolar mania. *Comprehensive Psychiatry*. 2012;53(8):1110-1117.
68. Practice guideline for the treatment of patients with bipolar disorder. American Psychiatric Association. *The American journal of psychiatry*. 1994;151(12 Suppl):1-36.
69. Yatham LN, Kusumakar V, Calabrese JR, Rao R, Scarrow G, Kroeker G. Third generation anticonvulsants in bipolar disorder: a review of efficacy and summary of clinical recommendations. *The Journal of clinical psychiatry*. 2002;63(4):275-283.

70. Chengappa KN, Gershon S, Levine J. The evolving role of topiramate among other mood stabilizers in the management of bipolar disorder. *Bipolar disorders*. 2001;3(5):215-232.
71. Grunze H, Vieta E, Goodwin GM, et al. The World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the biological treatment of bipolar disorders: update 2009 on the treatment of acute mania. *The world journal of biological psychiatry : the official journal of the World Federation of Societies of Biological Psychiatry*. 2009;10(2):85-116.
72. Liu HY, Potter MP, Woodworth KY, et al. Pharmacologic treatments for pediatric bipolar disorder: a review and meta-analysis. *Journal of the American Academy of Child and Adolescent Psychiatry*. 2011;50(8):749-762.e739.
73. CDC. ADHD Key Findings. . 2016; <http://www.cdc.gov/ncbddd/adhd/features/key-findings-adhd72013.html>. Accessed 8/12, 2016.
74. Glassman AH, Pardell R, Woodring S. Cardiovascular effects of the standard tricyclic antidepressants. *Clinical chemistry*. 1988;34(5):856-858.
75. Grunze H, Vieta E, Goodwin GM, et al. The World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the biological treatment of bipolar disorders: update 2012 on the long-term treatment of bipolar disorder. *The world journal of biological psychiatry : the official journal of the World Federation of Societies of Biological Psychiatry*. 2013;14(3):154-219.
76. Hirschfeld RMA BC, Gitlin MJ, Keck PE, Suppes T, Thase ME, Wagner KD, Perlis RH. Practice guideline for the treatment of patients with bipolar disorder. 2002. https://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/bipolar.pdf. Accessed 8/8/16.
77. Kendall T, Morriss R, Mayo-Wilson E, Marcus E. Assessment and management of bipolar disorder: summary of updated NICE guidance. *BMJ (Clinical research ed.)*. 2014;349:g5673.
78. McClellan J, Kowatch R, Findling RL. Practice parameter for the assessment and treatment of children and adolescents with bipolar disorder. *Journal of the American Academy of Child and Adolescent Psychiatry*. 2007;46(1):107-125.
79. Yatham LN, Kennedy SH, Parikh SV, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) collaborative update of CANMAT guidelines for the management of patients with bipolar disorder: update 2013. *Bipolar disorders*. 2013;15(1):1-44.
80. Kendall T, Morriss R, Mayo-Wilson E, et al. NICE guidance on psychological treatments for bipolar disorder. *The lancet. Psychiatry*. 2016;3(4):317-320.
81. Korczak DJ. Use of selective serotonin reuptake inhibitor medications for the treatment of child and adolescent mental illness. *Paediatrics and Child Health (Canada)*. 2013;18(9):1-6.
82. Group TMOBDW. VA/DoD Clinical Practice Guideline for Management of Bipolar Disorder in Adults. 2010. http://www.healthquality.va.gov/guidelines/MH/bd/bd_305_full.pdf.
83. Suppes T, Dennehy EB, Hirschfeld RM, et al. The Texas implementation of medication algorithms: update to the algorithms for treatment of bipolar I disorder. *The Journal of clinical psychiatry*. 2005;66(7):870-886.

84. Schizophrenia. Statistics. 2016; <http://www.nimh.nih.gov/health/statistics/prevalence/schizophrenia.shtml>. Accessed 8/4, 2016.
85. CDC. Databriefs. 2016; <http://www.cdc.gov/nchs/data/databriefs/db172.ht>. Accessed 8/12, 2016.
86. Fleischhacker WW, Kane JM, Geier J, et al. Completed and attempted suicides among 18,154 subjects with schizophrenia included in a large simple trial. *The Journal of clinical psychiatry*. 2014;75(3):e184-190.
87. Hasan A, Falkai P, Wobrock T, et al. World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for Biological Treatment of Schizophrenia. Part 3: Update 2015 Management of special circumstances: Depression, Suicidality, substance use disorders and pregnancy and lactation. *The world journal of biological psychiatry : the official journal of the World Federation of Societies of Biological Psychiatry*. 2015;16(3):142-170.
88. Hasan A, Falkai P, Wobrock T, et al. World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for biological treatment of schizophrenia, part 2: update 2012 on the long-term treatment of schizophrenia and management of antipsychotic-induced side effects. *The world journal of biological psychiatry : the official journal of the World Federation of Societies of Biological Psychiatry*. 2013;14(1):2-44.
89. Hasan A, Falkai P, Wobrock T, et al. World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for Biological Treatment of Schizophrenia, part 1: update 2012 on the acute treatment of schizophrenia and the management of treatment resistance. *The world journal of biological psychiatry : the official journal of the World Federation of Societies of Biological Psychiatry*. 2012;13(5):318-378.
90. van Os J, Kapur S. Schizophrenia. *Lancet*. 2009;374(9690):635-645.
91. Picchioni MM, Murray RM. Schizophrenia. *BMJ (Clinical research ed.)*. 2007;335(7610):91-95.
92. Holder SD, Wayhs A. Schizophrenia. *American family physician*. 2014;90(11):775-782.
93. Lehman AF, Lieberman JA, Dixon LB, et al. Practice guideline for the treatment of patients with schizophrenia, second edition. *The American journal of psychiatry*. 2004;161(2 Suppl):1-56.
94. NICE. Psychosis and Schizophrenia in Adults. 2014. <https://www.nice.org.uk/guidance/cg178/evidence/full-guideline-490503565>.
95. McClellan J, Stock S. Practice parameter for the assessment and treatment of children and adolescents with schizophrenia. *Journal of the American Academy of Child and Adolescent Psychiatry*. 2013;52(9):976-990.
96. Srisurapanont M, Suttajit S, Maneeton N, Maneeton B. Efficacy and safety of aripiprazole augmentation of clozapine in schizophrenia: a systematic review and meta-analysis of randomized-controlled trials. *Journal of psychiatric research*. 2015;62:38-47.
97. Muscatello MR, Pandolfo G, Mico U, et al. Augmentation of clozapine with ziprasidone in refractory schizophrenia: a double-blind, placebo-controlled study. *Journal of clinical psychopharmacology*. 2014;34(1):129-133.
98. Zink M, Kuwilsky A, Krumm B, Dressing H. Efficacy and tolerability of ziprasidone versus risperidone as augmentation in patients partially responsive to clozapine: a randomised controlled clinical trial. *Journal of psychopharmacology (Oxford, England)*. 2009;23(3):305-314.

99. Genc Y, Taner E, Candansayar S. Comparison of clozapine-amisulpride and clozapine-quetiapine combinations for patients with schizophrenia who are partially responsive to clozapine: a single-blind randomized study. *Adv Ther.* 2007;24(1):1-13.
100. Freudenreich O, Henderson DC, Walsh JP, Culhane MA, Goff DC. Risperidone augmentation for schizophrenia partially responsive to clozapine: a double-blind, placebo-controlled trial. *Schizophrenia research.* 2007;92(1-3):90-94.
101. Honer WG, Thornton AE, Chen EY, et al. Clozapine alone versus clozapine and risperidone with refractory schizophrenia. *N Engl J Med.* 2006;354(5):472-482.
102. Kaye NS. Ziprasidone augmentation of clozapine in 11 patients. *The Journal of clinical psychiatry.* 2003;64(2):215-216.
103. Rajarethinam R, Gilani S, Tancer M, DeQuardo J. Augmentation of clozapine partial responders with conventional antipsychotics. *Schizophrenia research.* 2003;60(1):97-98.
104. Kreyenbuhl J, Buchanan RW, Dickerson FB, Dixon LB. The Schizophrenia Patient Outcomes Research Team (PORT): updated treatment recommendations 2009. *Schizophrenia bulletin.* 2010;36(1):94-103.
105. Cullen BA, McGinty EE, Zhang Y, et al. Guideline-concordant antipsychotic use and mortality in schizophrenia. *Schizophrenia bulletin.* 2013;39(5):1159-1168.
106. Link JO, Taylor JG, Xu L, et al. Discovery of ledipasvir (GS-5885): a potent, once-daily oral NS5A inhibitor for the treatment of hepatitis C virus infection. *Journal of medicinal chemistry.* 2014;57(5):2033-2046.
107. Miller A, Hall CS, Buchanan RW, et al. The Texas Medication Algorithm Project antipsychotic algorithm for schizophrenia: 2003 update. *The Journal of clinical psychiatry.* 2004;65(4):500-508.
108. L FE. Epidemiology and classification of diabetic neuropathy. 2016. http://www.uptodate.com.ezproxy.lib.utah.edu/contents/epidemiology-and-classification-of-diabetic-neuropathy?source=see_link.
109. Microvascular complications and foot care. *Diabetes Care.* 2015. http://care.diabetesjournals.org/content/38/Supplement_1/S58.
110. Boulton AJ, Vinik AI, Arezzo JC, et al. Diabetic neuropathies: a statement by the American Diabetes Association. *Diabetes Care.* 2005;28(4):956-962.
111. Brill V, England J, Franklin GM, et al. Evidence-based guideline: Treatment of painful diabetic neuropathy: report of the American Academy of Neurology, the American Association of Neuromuscular and Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation. *PM & R : the journal of injury, function, and rehabilitation.* 2011;3(4):345-352, 352.e341-321.
112. Neuropathic pain in adults: pharmacological management in non-specialist settings. *CG173.* 2013. <https://www.nice.org.uk/guidance/cg173>.
113. 1):S1-S212 CDACPGECDCACPGftPaMoDiCCJDs.
114. Committee CPGE. Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada. . 2013. <http://guidelines.diabetes.ca/fullguidelines>.
115. Trevor AJ, Katzung BG, Kruidering-Hall M. Antidepressants. *Katzung & Trevor's Pharmacology: Examination & Board Review, 11e.* New York, NY: McGraw-Hill Education; 2015.
116. NL. B. Chapter 16. Antidepressants, Tricyclic. In: eds. OK, ed. *Poisoning & Drug Overdose, 6e.* New York, NY: McGraw-Hill;; 2012: <http://accessmedicine.mhmedical.com/content.aspx?bookid=391&Sectionid=42069830>.

117. Craig NJ. Tricyclic and Tetracyclic Drugs. In: F SA, ed. *Essentials of Clinical Psychopharmacology*. 3rd Edition ed. Arlington, VA: American Psychiatric Publishing; 2013.
118. Fiedorowicz JG, Swartz KL. The role of monoamine oxidase inhibitors in current psychiatric practice. *Journal of psychiatric practice*. 2004;10(4):239-248.
119. K G. MAOIs: Overview and History. 2014. <http://www.psychotropical.com/maois-overview-history>.
120. Kerr G, McGuffie A, Wilkie S. Tricyclic antidepressant overdose: a review. *Emergency medicine journal : EMJ*. 2001;18(4):236-241.
121. Jarvis MR. Clinical pharmacokinetics of tricyclic antidepressant overdose. *Psychopharmacology bulletin*. 1991;27(4):541-550.
122. Ponto LB, Perry PJ, Liskow BI, Seaba HH. Drug therapy reviews: tricyclic antidepressant and monoamine oxidase inhibitor combination therapy. *American journal of hospital pharmacy*. 1977;34(9):954-961.
123. Tylee A, Walters P. Onset of action of antidepressants. *BMJ : British Medical Journal*. 2007;334(7600):911-912.
124. D'Amico D, Tepper SJ. Prophylaxis of migraine: general principles and patient acceptance. *Neuropsychiatric Disease and Treatment*. 2008;4(6):1155-1167.
125. Ziegler D. Painful Diabetic Neuropathy. *Diabetes Care*. 2009;32(suppl 2):S414.
126. Webster LB, D.: Barrett, A.: Paterson, C.: Bortey, E.: Forbes, W. Analysis of opioid-mediated analgesia in studies with methylnaltrexone for opioid-induced constipation in patients with chronic noncancer pain. *Journal of pain*. 2015;16(4 suppl. 1):S92. <http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/895/CN-01080895/frame.html>.
127. Gillman PK. Tricyclic antidepressant pharmacology and therapeutic drug interactions updated. *British journal of pharmacology*. 2007;151(6):737-748.
128. Gaudiano BA, Herbert JD. Methodological issues in clinical trials of antidepressant medications: perspectives from psychotherapy outcome research. *Psychotherapy and psychosomatics*. 2005;74(1):17-25.
129. Kirsch I. Antidepressants and the Placebo Effect. *Zeitschrift Fur Psychologie*. 2014;222(3):128-134.
130. Magni LR, Purgato M, Gastaldon C, et al. Fluoxetine versus other types of pharmacotherapy for depression. *The Cochrane database of systematic reviews*. 2013(7):Cd004185.
131. Rayner L, Price A, Evans A, Valsraj K, Higginson IJ, Hotopf M. Antidepressants for depression in physically ill people. *The Cochrane database of systematic reviews*. 2010(3):Cd007503.
132. Guaiana G, Barbui C, Hotopf M. Amitriptyline for depression. *The Cochrane database of systematic reviews*. 2007(3):Cd004186.
133. Mittmann N, Herrmann N, Einarson TR, et al. The efficacy, safety and tolerability of antidepressants in late life depression: a meta-analysis. *Journal of affective disorders*. 1997;46(3):191-217.
134. Gerson S, Belin TR, Kaufman A, Mintz J, Jarvik L. Pharmacological and psychological treatments for depressed older patients: a meta-analysis and overview of recent findings. *Harvard review of psychiatry*. 1999;7(1):1-28.

135. Wilkinson P, Izmeth Z. Continuation and maintenance treatments for depression in older people. *The Cochrane database of systematic reviews*. 2012;11:Cd006727.
136. Hazell P, Mirzaie M. Tricyclic drugs for depression in children and adolescents. *The Cochrane database of systematic reviews*. 2013(6):Cd002317.
137. Ipser JC, Stein DJ, Hawkrigde S, Hoppe L. Pharmacotherapy for anxiety disorders in children and adolescents. *The Cochrane database of systematic reviews*. 2009(3):Cd005170.
138. Ostuzzi G, Matcham F, Dauchy S, Barbui C, Hotopf M. Antidepressants for the treatment of depression in people with cancer. *The Cochrane database of systematic reviews*. 2015(6):Cd011006.
139. Furukawa TA, McGuire H, Barbui C. Meta-analysis of effects and side effects of low dosage tricyclic antidepressants in depression: systematic review. *BMJ (Clinical research ed.)*. 2002;325(7371):991.
140. Glazener CMA, Evans JHC. Desmopressin for nocturnal enuresis in children. *Cochrane Database of Systematic Reviews*. 2002(3).
141. Glazener CM, Evans JH, Cheuk DK. Complementary and miscellaneous interventions for nocturnal enuresis in children. *The Cochrane database of systematic reviews*. 2005(2):Cd005230.
142. Richards BL, Whittle SL, Buchbinder R. Antidepressants for pain management in rheumatoid arthritis. *The Cochrane database of systematic reviews*. 2011(11):Cd008920.
143. Moore RA, Derry S, Aldington D, Cole P, Wiffen PJ. Amitriptyline for neuropathic pain in adults. *The Cochrane database of systematic reviews*. 2015(7):Cd008242.
144. Derry S, Wiffen PJ, Aldington D, Moore RA. Nortriptyline for neuropathic pain in adults. *The Cochrane database of systematic reviews*. 2015;1:Cd011209.
145. Hearn L, Moore RA, Derry S, Wiffen PJ, Phillips T. Desipramine for neuropathic pain in adults. *The Cochrane database of systematic reviews*. 2014(9):Cd011003.
146. Hearn L, Derry S, Phillips T, Moore RA, Wiffen PJ. Imipramine for neuropathic pain in adults. *The Cochrane database of systematic reviews*. 2014(5):Cd010769.
147. Banzi R, Cusi C, Randazzo C, Sterzi R, Tedesco D, Moja L. Selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) for the prevention of tension-type headache in adults. *The Cochrane database of systematic reviews*. 2015(5):Cd011681.
148. Banzi R, Cusi C, Randazzo C, Sterzi R, Tedesco D, Moja L. Selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) for the prevention of migraine in adults. *Cochrane Database of Systematic Reviews*. 2015(4).
149. Otasowie J, Castells X, Ehimare UP, Smith CH. Tricyclic antidepressants for attention deficit hyperactivity disorder (ADHD) in children and adolescents. *The Cochrane database of systematic reviews*. 2014(9):Cd006997.
150. Hurwitz R, Blackmore R, Hazell P, Williams K, Woolfenden S. Tricyclic antidepressants for autism spectrum disorders (ASD) in children and adolescents. *The Cochrane database of systematic reviews*. 2012(3):Cd008372.
151. Ruepert L, Quartero AO, de Wit NJ, van der Heijden GJ, Rubin G, Muris JW. Bulking agents, antispasmodics and antidepressants for the treatment of irritable bowel syndrome. *The Cochrane database of systematic reviews*. 2011(8):Cd003460.

152. Schneeweiss S, Patrick AR, Solomon DH, et al. Comparative safety of antidepressant agents for children and adolescents regarding suicidal acts. *Pediatrics*. 2010;125(5):876-888.
153. Schneeweiss S, Patrick AR, Solomon DH, et al. Variation in the risk of suicide attempts and completed suicides by antidepressant agent in adults: a propensity score-adjusted analysis of 9 years' data. *Archives of general psychiatry*. 2010;67(5):497-506.
154. Holtzheimer PE, 3rd, Nemeroff CB. Advances in the treatment of depression. *NeuroRx : the journal of the American Society for Experimental NeuroTherapeutics*. 2006;3(1):42-56.
155. Gilman Ga. The Pharmacologic Basis of Therapeutics. In: Laurence L. Brunton BAC, Björn C. Knollmann ed. China2011.
156. Alvarez W, Pickworth KK. Safety of Antidepressant Drugs in the Patient with Cardiac Disease: A Review of the Literature. *Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy*. 2003;23(6):754-771.
157. Sheehan DV, Keene MS, Eaddy M, Krulewicz S, Kraus JE, Carpenter DJ. Differences in medication adherence and healthcare resource utilization patterns: older versus newer antidepressant agents in patients with depression and/or anxiety disorders. *CNS drugs*. 2008;22(11):963-973.
158. Gagne JJ, Patrick AR, Mogun H, Solomon DH. Antidepressants and fracture risk in older adults: a comparative safety analysis. *Clinical pharmacology and therapeutics*. 2011;89(6):880-887.
159. Jick SS, Li L. Antidepressant drug use and risk of venous thromboembolism. *Pharmacotherapy*. 2008;28(2):144-150.
160. Ropper AH, Samuels MA, Klein JP. Chapter 43. Disorders of the Nervous System Caused by Drugs, Toxins, and Chemical Agents. *Adams and Victor's Principles of Neurology, 10e*. New York, NY: The McGraw-Hill Companies; 2014.
161. Thornton WE. Tricyclic antidepressant and cardiovascular drug interactions. *American family physician*. 1979;20(1):97-99.
162. Cocco G, Agué C. Interactions between cardioactive drugs and antidepressants. *European journal of clinical pharmacology*. 1977;11(5):389-393.
163. Gillman PK. Monoamine oxidase inhibitors, opioid analgesics and serotonin toxicity. *Br J Anaesth*. 2005;95(4):434-441.
164. Preskorn SH, Flockhart D. 2006 Guide to psychiatric drug interactions. *Primary Psychiatry*. 2006;13(4):35-64.
165. Pacher P, Kecskemeti V. Cardiovascular Side Effects of New Antidepressants and Antipsychotics: New Drugs, old Concerns? *Current pharmaceutical design*. 2004;10(20):2463-2475.
166. Brozek JL, Akl EA, Alonso-Coello P, et al. Grading quality of evidence and strength of recommendations in clinical practice guidelines. Part 1 of 3. An overview of the GRADE approach and grading quality of evidence about interventions. *Allergy*. 2009;64(5):669-677.
167. Brozek JL, Akl EA, Compalati E, et al. Grading quality of evidence and strength of recommendations in clinical practice guidelines part 3 of 3. The GRADE approach to developing recommendations. *Allergy*. 2011;66(5):588-595.