Antidepressant Comparison: Advanced Clinical Reference

💊 Comparative Pharmacology and Clinical Applications

This comprehensive reference provides detailed comparisons between antidepressant classes for psychiatric prescribers, with evidence-based clinical pearls and monitoring recommendations.

🧠 Mechanism of Action and Receptor Pharmacology

CLASS	PRIMARY MECHANISM	RECEPTOR PROFILE	CLINICAL IMPLICATIONS
🔵 SSRIs (Chu & Wadhwa, 2023)	Serotonin reuptake inhibition	• 5-HT transporter: + +++ • NE transporter: +/0 • DA transporter: 0 • 5-HT_2C: 0/+ • H_1: 0/+	• Delayed onset (2-4 weeks) • Sexual dysfunction common • Minimal weight gain (except paroxetine) • Low lethality in overdose
🟣 SNRIs (Sansone & Sansone, 2014)	Serotonin and norepinephrine reuptake inhibition	• 5-HT transporter: + +++ • NE transporter: ++/ ++++ • DA transporter: 0/+ • α_1: + • H_1: 0/+	• May help somatic symptoms • Blood pressure effects • Potentially more activating • Withdrawal symptoms common
🟠 NDRIs (Yu et al., 2020)	Norepinephrine and dopamine reuptake inhibition	• NE transporter: ++ • DA transporter: ++ • 5-HT transporter: 0 • nAChR: + • H_1: 0	• Activating/energizing • Low sexual dysfunction • Weight neutral/loss • Seizure risk at higher doses
🟢 TCAs (Moraczewski & Aedma, 2023)	Multiple monoamine reuptake inhibition and receptor antagonism	• 5-HT transporter: + ++ • NE transporter: +++ • H_1: +++ • α_1: +++ • mAChR: +++	• Significant side effects • Cardiac conduction effects • Anticholinergic effects • High lethality in

			overdose

🟡 MAOIs Monoamine oxidase inhibition

CLASS	PRIMARY MECHANISM	RECEPTOR PROFILE	CLINICAL IMPLICATIONS
		• MAO-A: ++++ • MAO-B: ++/++++ • Tyramine metabolism: ↓↓↓↓ • Indirect effect on all monoamines	• Dietary restrictions • Drug interactions • Hypertensive crisis risk • Effective for atypical depression (Laban & Saadabadi, 2023)
🔴 Atypical Antidepressants	Various mechanisms	• Varies by agent • Often multimodal • Receptor-specific effects • Less reuptake inhibition	• Unique side effect profiles • Often used for specific symptoms • Variable sexual effects • Variable weight effects

📊 Comparative Efficacy for Major Depressive Disorder

MEDICATION	OVERALL EFFICACY	MELANCHOLIC FEATURES	ATYPICAL FEATURES	ANXIOUS DISTRESS	MIXED FEATURES
🔵 Escitalopram (Lam & Ali, 2011)	★★★★☆ • First-line • Well tolerated • Consistent efficacy	★★★☆☆ • Moderate efficacy • May need higher doses • Often requires augmentation	★★★☆☆ • Moderate efficacy • Weight gain possible • Sedation can help hypersomnia	★★★★☆ • Strong anxiolytic effects • Good for comorbid anxiety • May need higher doses	★★☆☆☆ • Limited efficacy • May worsen mixed symptoms • Monitor for activation
🔵 Sertraline (Adjei et al., 2023)	★★★★☆ • First-line • Well tolerated • Mild DA effects at higher doses	★★★☆☆ • Moderate efficacy • Higher doses more effective • DA effects may help	★★★☆☆ • Moderate efficacy • Less weight gain than paroxetine • Activating at higher doses	★★★★☆ • Strong anxiolytic effects • FDA-approved for multiple anxiety disorders • Good for comorbid	★★☆☆☆ • Limited efficacy • May worsen mixed symptoms • Monitor for activation

				PTSD/ OCD	

Fluoxetine(Adjei et al., 2023)

★★★★☆ • First-line • Activating profile • Long half life

★★★☆☆ • Moderate efficacy • Activating properties helpful • May help psychomotor retardation

2 ★★★☆☆ • Moderate efficacy • Less effective for hypersomnia • May worsen insomnia

★★★☆☆ • Moderate anxiolytic effects • Initial activation may worsen anxiety • Good for comorbid OCD • Better than other SSRIs • Approved for bipolar depression with olanzapine

★★★☆☆

MEDICATION	OVERALL EFFICACY	MELANCHOLIC FEATURES	ATYPICAL FEATURES	ANXIOUS DISTRESS	MIXED FEATURES
					• Monitor for activation
Venlafaxine (de Silva & Hanwella, 2012)	★★★★★ • Possibly superior efficacy • Dose dependent NE effects • Higher doses more effective	★★★★☆ • Strong efficacy • Dual-action beneficial • Good for severe depression	★★★☆☆ • Moderate efficacy • Less effective for hypersomnia • Activating properties	★★★★☆ • Strong anxiolytic effects • FDA-approved for multiple anxiety disorders • Initial activation may worsen anxiety	★★☆☆☆ • Limited efficacy • May worsen mixed symptoms • Monitor for activation/ switching
Duloxetine (Gartlehner et al., 2009)	★★★★☆ • First-line • Balanced 5- HT/NE effects • Good for pain syndromes	★★★★☆ • Strong efficacy • Dual-action beneficial • Good for somatic symptoms	★★★☆☆ • Moderate efficacy • Less weight gain than paroxetine • Less effective for hypersomnia	★★★★☆ • Strong anxiolytic effects • FDA-approved for GAD • Good for somatic anxiety	★★☆☆☆ • Limited efficacy • May worsen mixed symptoms • Monitor for activation/ switching

Bupropion (Maneeton et al., 2013)	★★★☆☆ • Second-line • Activating profile • Less effective than SSRIs/SNRIs	★★★☆☆ • Moderate efficacy • Helpful for fatigue/ psychomotor retardation • Less effective for core mood symptoms	★★★★☆ • Strong efficacy • Helpful for hypersomnia/ fatigue • Weight neutral/loss	★★☆☆☆ • May worsen anxiety • Activating properties problematic • Not for comorbid anxiety	★★★★☆ • Better for mixed features • Less risk of switching • Helpful for ADHD symptoms
Amitriptyline (Mathur et al., 2002)	★★★★☆ • Effective but not first-line • Significant side effects • Good for pain/ insomnia	★★★★★ • Very strong efficacy • Historically preferred • Sedation helps sleep disturbance	★★★☆☆ • Moderate efficacy • Sedation helps hypersomnia • Weight gain problematic	★★★☆☆ • Moderate anxiolytic effects • Sedation helps anxiety • Initial anticholinergic effects may worsen	★★☆☆☆ • Limited efficacy • May worsen mixed symptoms • Higher switch risk

Phenelzine ★★★★★ • Very effective • Not first-line due to safety ★★★☆☆ • Moderate efficacy • Less preferred than for atypical ★★★★★ • Superior efficacy • Historically preferred ★★★★☆ • Strong anxiolytic effects • Good for social anxiety ★★☆☆☆ • Limited efficacy • May worsen mixed

MEDICATION	OVERALL EFFICACY	MELANCHOLIC FEATURES	ATYPICAL FEATURES	ANXIOUS DISTRESS	MIXED FEATURES
	• Good for treatment resistant cases	• Historically used for severe cases	• Helps hyperphagia/ hypersomnia	• Good for panic disorder	symptoms • High switch risk
Mirtazapine (Mathur et al., 2002)	★★★★☆ • Effective • Rapid onset of sleep/ appetite effects • Unique mechanism	★★★☆☆ • Moderate efficacy • Sedation helps insomnia • Weight gain helps anorexia	★★★★☆ • Strong efficacy • Sedation helps hypersomnia • Weight gain problematic	★★★★☆ • Strong anxiolytic effects • $5\text{-HT}_2A/_2C$ blockade beneficial • Sedation helps anxiety	★★★☆☆ • Better than SSRIs/SNRIs • Less activation • Monitor for sedation

Pharmacokinetics and Dosing Considerations

MEDICATION	HALF-LIFE	METABOLISM	DOSING STRATEGY	THERAPEUTIC CONSIDERATIONS
☐ Escitalopram (Drugs.com, 2019)	• 27-32 hours • Active S-enantiomer • Steady state: 7-10 days	• CYP2C19 (major) • CYP3A4 (minor) • Few active metabolites • Minimal inhibition of CYPs	• Start: 10mg daily • Therapeutic: 10-20mg daily • Elderly: 5-10mg daily • Once daily dosing	• Superior efficacy to citalopram • Better tolerability than citalopram • Less dose-dependent QT prolongation • Fewer drug interactions than most
☐ Sertraline (Singh & Saadabadi, 2023)	• 26 hours • N-desmethylsertraline: 62-104 hours • Steady state: 7 days	• Multiple CYPs • CYP2B6, 2C9, 2C19, 2D6, 3A4 • Weak inhibitor of CYP2D6 • Moderate inhibitor of CYP2B6	• Start: 50mg daily • Therapeutic: 50-200mg daily • Elderly: 25-50mg daily • Once daily dosing	• Mild dopaminergic effects at higher doses • Dose-dependent efficacy • Fewer drug interactions than most SSRIs • Good choice with polypharmacy
☐ Fluoxetine (Durbin, 2022)	• 2-4 days • Norfluoxetine: 7-15 days • Steady state: 4-5 weeks	• CYP2D6 (major) • CYP2C9, 3A4 (minor) • Strong inhibitor of CYP2D6 • Moderate inhibitor of CYP2C9, 3A4	• Start: 20mg daily • Therapeutic: 20-80mg daily • Elderly: 10mg daily • Once daily dosing	• Long half-life beneficial for adherence • Significant drug interactions • Weekly dosing possible for maintenance • Activating profile

MEDICATION	HALF-LIFE	METABOLISM	DOSING STRATEGY	THERAPEUTIC CONSIDERATIONS
☐ Venlafaxine (Singh & Saadabadi, 2024)	• 5 hours • O desmethylvenlafaxine: 11 hours • Steady state: 3-4 days	• CYP2D6 (major) • CYP3A4 (minor) • Active metabolite (desvenlafaxine) • Weak inhibitor of CYP2D6	• Start: 37.5-75mg daily • Therapeutic: 150-375mg daily • Elderly: 37.5mg daily • BID dosing (IR), daily (XR)	• Dose-dependent NE effects (>150mg) • XR formulation better tolerated • Significant discontinuation syndrome • BP monitoring at higher doses

Duloxetine	• 12 hours • No significant active metabolites • Steady state: 3-5 days	• CYP1A2 (major) • CYP2D6 (major) • Moderate inhibitor of CYP2D6 • Smoking reduces levels (CYP1A2)	• Start: 30mg daily • Therapeutic: 60-120mg daily • Elderly: 30mg daily • Once or twice daily dosing	• Balanced 5-HT/NE effects at all doses • Enteric coating (don't crush/chew) • Take consistently with/ without food • FDA-approved for pain conditions
Bupropion	• IR: 14 hours • SR: 21 hours • XL: 24 hours • Active metabolites: hydroxybupropion	• CYP2B6 (major) • Multiple active metabolites • Moderate inhibitor of CYP2D6 • Minimal effect on other CYPs	• IR: 100mg TID (max 450mg/ day) • SR: 150mg BID (max 400mg/day) • XL: 150-300mg daily • Allow 8 hours between doses	• Seizure risk dose dependent • Different formulations not equivalent mg-per mg • Morning dosing to prevent insomnia • Avoid in eating disorders (seizure risk)
Amitriptyline (Thour & Marwaha, 2023)	• 10-50 hours • Nortriptyline: 18-44 hours • Steady state: 4-8 days	• CYP2D6 (major) • CYP2C19, 3A4 (minor) • Active metabolite (nortriptyline) • Substrate of P glycoprotein	• Start: 25-50mg at bedtime • Therapeutic: 75-300mg daily • Elderly: 10-25mg at bedtime • Once daily dosing at bedtime	• Therapeutic plasma level: 80-200 ng/mL • Significant anticholinergic effects • Significant antihistaminic effects • Significant cardiac effects
Phenelzine	• 11.6 hours • MAO recovery: 2 weeks • Steady state: 7-10 days • Acetylation (major) • MAO inhibition	irreversible • Multiple	• Therapeutic: 45-90mg daily • Elderly: 15mg • Dietary tyramine	restrictions • Numerous drug interactions • 2-week washout

MEDICATION	HALF-LIFE	METABOLISM	DOSING STRATEGY	THERAPEUTIC CONSIDERATIONS
		metabolic pathways • Minimal CYP involvement	daily-BID • Divided dosing (TID QID)	before/after other antidepressants • BP monitoring required

Mirtazapine (Jilani et al., 2024)	• 20-40 hours • Demethylmirtazapine: similar • Steady state: 5-6 days	• CYP1A2, 2D6, 3A4 • Multiple pathways • Minimal effect on CYPs • Few significant interactions	• Start: 15mg at bedtime • Therapeutic: 15-45mg daily • Elderly: 7.5-15mg at bedtime • Once daily dosing at bedtime	• Sedation decreases at higher doses • Weight gain dose dependent • Orally disintegrating tablet available • Less sexual dysfunction than SSRIs

Adverse Effects and Management Strategies

MEDICATION CLASS	COMMON ADVERSE EFFECTS	SERIOUS ADVERSE EFFECTS	MANAGEMENT STRATEGIES	CONTRAINDICATIONS
SSRIs (Santarsieri & Schwartz, 2015)	• Nausea/GI distress • Sexual dysfunction • Insomnia/ somnolence • Headache • Activation/ jitteriness	• Serotonin syndrome • Hyponatremia • Abnormal bleeding • QT prolongation (citalopram) • Discontinuation syndrome	• GI effects: take with food, temporary • Sexual dysfunction: dose reduction, drug holiday, add bupropion • Insomnia: morning dosing • Activation: start low, titrate slowly • Discontinuation: taper gradually	• MAOIs within 14 days • Pimozide (with certain SSRIs) • Thioridazine (with CYP2D6 inhibitors) • Linezolid, IV methylene blue • Congenital long QT (citalopram)
SNRIs (Santarsieri & Schwartz, 2015)	• Nausea/GI distress • Sexual dysfunction • Increased blood pressure • Headache • Dry mouth	• Serotonin syndrome • Hyponatremia • Abnormal bleeding • Hepatotoxicity (duloxetine) • Severe discontinuation syndrome	• GI effects: take with food, temporary • BP effects: monitor BP, dose reduction • Sexual dysfunction: similar to SSRIs • Discontinuation: taper very gradually • Hepatotoxicity: LFT monitoring	• MAOIs within 14 days • Uncontrolled hypertension • Severe renal impairment (duloxetine) • Hepatic impairment (duloxetine) • Linezolid, IV methylene blue
Bupropion	• Insomnia	• Seizures (dose	• Insomnia: morning	• Seizure disorder

• Headache dependent) dosing, avoid evening • Current/prior bulimia or

MEDICATION CLASS	COMMON ADVERSE EFFECTS	SERIOUS ADVERSE EFFECTS	MANAGEMENT STRATEGIES	CONTRAINDICATIONS
	• Dry mouth • Nausea • Anxiety/ agitation	• Hypertension • Psychosis (rare) • Angle-closure glaucoma • Allergic reactions	• Seizure risk: stay within dose limits • Anxiety: start low, titrate slowly • Dry mouth: hydration, sugar-free gum • Headache: usually temporary	anorexia • MAOIs within 14 days • Abrupt discontinuation of alcohol/sedatives • Severe hepatic/renal impairment
☐ TCAs (Moraczewski & Aedma, 2023)	• Anticholinergic effects • Sedation • Orthostatic hypotension • Weight gain • Cardiac conduction changes	• Cardiac arrhythmias • Seizures in overdose • Severe anticholinergic toxicity • Paralytic ileus • Serotonin syndrome (with other agents)	• Anticholinergic: hydration, sugar-free gum • Orthostatic hypotension: rise slowly, hydration • Cardiac: baseline ECG, monitoring • Sedation: bedtime dosing • Weight gain: diet, exercise, monitoring	• Recent MI • QT prolongation • Heart block • MAOIs within 14 days • Severe prostatic hypertrophy
☐ MAOIs (Laban & Saadabadi, 2023)	• Orthostatic hypotension • Insomnia • Weight gain • Sexual dysfunction • Edema	• Hypertensive crisis • Serotonin syndrome • Hepatotoxicity • Hypoglycemia • Peripheral neuropathy	• Dietary restrictions: low-tyramine diet • Orthostatic hypotension: rise slowly, hydration • Insomnia: morning dosing • Edema: sodium restriction, elevation • BP monitoring: home monitoring	• Pheochromocytoma • Carcinoid tumor • Serotonergic medications • Sympathomimetics • Aged/fermented foods

Mirtazapine	• Sedation • Weight gain • Dry mouth • Constipation • Dizziness	• Agranulocytosis (rare) • Severe neutropenia • Seizures (rare) • Serotonin syndrome (with other agents) • Angle-closure glaucoma	• Sedation: bedtime dosing, may improve • Weight gain: diet, exercise, monitoring • Dry mouth: hydration, sugar-free gum • Higher doses less sedating (receptor profile) • Orally disintegrating tablet for adherence	• MAOIs within 14 days • Severe hepatic/renal impairment (relative) • History of agranulocytosis • Angle-closure glaucoma • Severe CNS depression

Drug Interactions and Combination Strategies

MEDICATION CLASS	SIGNIFICANT INTERACTIONS	EFFECT ON OTHER DRUGS	COMBINATION STRATEGIES	PREGNANCY CONSIDERATIONS
SSRIs (Dobrea et al., 2024)	• MAOIs: serotonin syndrome • TCAs: ↑ TCA levels • Warfarin: ↑ bleeding risk • Tramadol: seizure/ serotonin syndrome risk • NSAIDs: ↑ bleeding risk	• Fluoxetine/ paroxetine: strong CYP2D6 inhibition • Fluvoxamine: strong CYP1A2, 2C19 inhibition • Sertraline: mild moderate CYP2D6 inhibition • Escitalopram: minimal CYP inhibition	• With bupropion: ↓ sexual dysfunction • With mirtazapine: ↓ sexual dysfunction, ↑ efficacy • With antipsychotics: monitor for ↑ levels • With anticonvulsants: generally safe • With stimulants: monitor for serotonin syndrome	• Category C • Paroxetine: Category D • Third trimester: PPHN risk, neonatal adaptation syndrome • Breastfeeding: sertraline preferred • Pregnancy registries available

SNRIs (Leonard, 2024)	• MAOIs: serotonin syndrome • TCAs: ↑ TCA levels • Warfarin: ↑ bleeding risk • Tramadol: seizure/ serotonin syndrome risk • NSAIDs: ↑ bleeding risk	• Duloxetine: moderate CYP2D6 inhibition • Venlafaxine: mild CYP2D6 inhibition • Desvenlafaxine: minimal CYP inhibition • Levomilnacipran: minimal CYP inhibition	• With bupropion: ↓ sexual dysfunction, caution with BP • With mirtazapine: ↓ sexual dysfunction, ↑ efficacy • With antipsychotics: monitor for ↑ levels • With anticonvulsants: generally safe • With stimulants: monitor BP, serotonin syndrome	• Category C • Third trimester: similar risks to SSRIs • Limited data compared to SSRIs • Breastfeeding: limited data • Pregnancy registries available
Bupropion • MAOIs: hypertensive crisis • Antipsychotics: ↑ seizure risk • Levodopa: ↑ adverse effects • Ritonavir: ↑	• Moderate CYP2D6 inhibition • Minimal effect on other CYPs • ↓ efficacy of	tamoxifen (CYP2D6) • ↑ levels of TCAs,	• With SSRIs/SNRIs: ↓ sexual dysfunction, ↑ efficacy • With antipsychotics: monitor for ↑	• Category C • Limited human data • No clear association with major malformations • Breastfeeding: limited data

MEDICATION CLASS	SIGNIFICANT INTERACTIONS	EFFECT ON OTHER DRUGS	COMBINATION STRATEGIES	PREGNANCY CONSIDERATIONS
	bupropion levels • Carbamazepine: ↓ bupropion levels	antipsychotics, β blockers	levels, seizure risk • With stimulants: monitor for ↑ BP, seizure risk • With anticonvulsants: monitor for ↓ bupropion efficacy • With NRT: approved for smoking cessation	• Pregnancy registry available

TCAs (Moraczewski & Aedma, 2023)	• MAOIs: serotonin syndrome, hyperpyrexia • SSRIs/SNRIs: ↑ TCA levels • Class I antiarrhythmics: ↑ cardiac effects • Anticholinergics: ↑ anticholinergic effects • Clonidine: hypertensive crisis	• Minimal effect on CYP enzymes • Additive effects with other anticholinergics • Additive effects with other sedatives • Additive QT prolongation • Antagonize guanethidine, clonidine	• With SSRIs: monitor TCA levels, start low • With antipsychotics: ↑ anticholinergic, sedation, QT • With anticonvulsants: monitor TCA levels • With stimulants: monitor for cardiac effects • With thyroid: augmentation strategy	• Category C • First trimester: possible ↑ malformations • Third trimester: neonatal adaptation syndrome • Breastfeeding: nortriptyline preferred • Limited recent data
MAOIs (Laban & Saadabadi, 2023)	• Serotonergic agents: fatal serotonin syndrome • Sympathomimetics: hypertensive crisis • Meperidine/ tramadol: fatal reactions • Dopaminergic agents: hypertensive crisis • Tyramine containing foods: hypertensive crisis	• Irreversible inhibition of MAO • ↑ effects of all monoamines • ↑ effects of sympathomimetics • ↑ effects of indirect-acting sympathomimetics • ↑ hypoglycemic effects of insulin/ sulfonylureas	• 2-week washout before/after other antidepressants • 5-week washout after fluoxetine • With stimulants: generally contraindicated • With anticonvulsants: generally safe • With bupropion: contraindicated	• Category C • Very limited human data • Generally avoided during pregnancy • Breastfeeding: generally avoided • Consider alternatives when possible
Mirtazapine	• MAOIs: serotonin syndrome • Clonidine: ↓ clonidine effects • Warfarin: rare cases • Minimal effect on CYP enzymes • No significant	inhibition or induction • With SSRIs/SNRIs: ↓	sexual dysfunction, ↑ efficacy • With bupropion:	• No clear association with major malformations • Category C • Limited human data

MEDICATION CLASS	SIGNIFICANT INTERACTIONS	EFFECT ON OTHER DRUGS	COMBINATION STRATEGIES	PREGNANCY CONSIDERATIONS

	of ↑ INR • Benzodiazepines: ↑ sedation • Alcohol: ↑ sedation	• Minimal effect on other drugs • Additive effects with other sedatives • Additive effects with other antihistamines	↓ weight gain, ↑ efficacy • With antipsychotics: monitor for ↑ sedation, weight • With anticonvulsants: generally safe • With TCAs: monitor for ↑ sedation, anticholinergic	• Breastfeeding: limited data • Consider risk/ benefit carefully

Neuropsychiatric Effects and Cognitive Impact

MEDICATION CLASS	COGNITIVE EFFECTS	NEUROPSYCHIATRIC EFFECTS	LONG-TERM CONSIDERATIONS	PATIENT SELECTION FACTORS
SSRIs (Rosenblatt et al., 2015)	• Minimal cognitive impairment • Possible word finding difficulties • Possible emotional blunting • Improved cognition with depression remission • Concentration difficulties (initial)	• Activation syndrome (10-25%) • Apathy/indifference • Emotional blunting • Rare SIADH/ hyponatremia • Rare extrapyramidal symptoms	• Generally well tolerated long-term • Sexual dysfunction often persists • Possible bone density effects • Possible weight gain over time • Discontinuation syndrome risk	• First-line for most depression • Good for anxious depression • Caution in bipolar disorder • Caution in elderly (falls, hyponatremia) • Avoid in sexual dysfunction
SNRIs (Rosenblatt et al., 2015)	• Minimal cognitive impairment • Possible improvement in attention • Possible emotional blunting • Improved cognition with depression remission • Concentration difficulties (initial)	• Activation syndrome (15-30%) • Increased blood pressure • Emotional blunting • Rare SIADH/ hyponatremia • Significant discontinuation syndrome	• BP monitoring recommended • Sexual dysfunction often persists • Discontinuation more difficult than SSRIs • Possible bone density effects • Generally stable efficacy	• Good for pain comorbidity • Good for fatigue/ low energy • Caution in uncontrolled hypertension • Caution in bipolar disorder • Avoid in significant cardiovascular disease

MEDICATION CLASS	COGNITIVE EFFECTS	NEUROPSYCHIATRIC EFFECTS	LONG-TERM CONSIDERATIONS	PATIENT SELECTION FACTORS
☐ Bupropion	• Minimal cognitive impairment • Possible improvement in attention • Activating effects • Improved concentration • No emotional blunting	• Insomnia (common) • Anxiety/agitation • Rare psychosis • Rare seizures (dose dependent) • No sexual dysfunction	• Weight neutral/ weight loss • No sexual dysfunction • No discontinuation syndrome • Stable efficacy long term • Continued seizure risk	• Good for fatigue/ low energy • Good with sexual dysfunction concerns • Good for atypical depression • Avoid in seizure disorders • Avoid in eating disorders
☐ TCAs (Moraczewski & Aedma, 2023)	• Significant cognitive impairment • Anticholinergic effects • Memory impairment • Confusion (especially elderly) • Sedation	• Delirium risk • Significant sedation • Rare induction of mania • Rare extrapyramidal symptoms • Cardiac conduction changes	• Anticholinergic burden increases over time • Tolerance to some side effects • Weight gain often continues • Cardiac monitoring recommended • Possible dementia risk	• Consider for treatment resistant cases • Good for pain syndromes • Avoid in elderly • Avoid in cardiac disease • Avoid in prostatic hypertrophy
☐ MAOIs (Laban & Saadabadi, 2023)	• Minimal cognitive impairment • Possible improvement in attention • Insomnia can affect cognition • Orthostatic hypotension effects • Improved cognition with depression remission	• Insomnia (common) • Orthostatic hypotension • Rare hypertensive crisis • Activation • Higher switch risk in bipolar	• Dietary restrictions ongoing • Drug interaction risk ongoing • Weight gain may continue • BP monitoring required • Peripheral neuropathy risk	• Consider for atypical depression • Consider for treatment resistant cases • Good for social anxiety • Avoid in non adherent patients • Avoid in elderly (falls risk)

Mirtazapine
• Sedation (dose dependent)
• Minimal cognitive impairment at higher doses
• Improved sleep architecture
• Antihistaminic effects
• Significant sedation (lower doses)
• Less sedation at higher doses
• Rare neutropenia • Vivid dreams
• Minimal activation 11

• Weight gain often continues
• Tolerance to sedation develops • Stable efficacy long term
• Minimal discontinuation syndrome
• Good for insomnia/anxiety • Good for appetite/weight loss
• Good for elderly (minimal drug interactions)
• Avoid with

MEDICATION CLASS	COGNITIVE EFFECTS	NEUROPSYCHIATRIC EFFECTS	LONG-TERM CONSIDERATIONS	PATIENT SELECTION FACTORS
	• Improved cognition with depression remission		• Minimal sexual dysfunction	significant weight concerns • Avoid when sedation problematic

Clinical Pearls and Practical Considerations

MEDICATION	UNIQUE ADVANTAGES	CLINICAL PEARLS	COMMON PITFALLS	PATIENT EDUCATION POINTS
Escitalopram (Boyce & Ma, 2021)	• Cleanest SSRI pharmacologically • Minimal drug interactions • Well-tolerated • Once daily dosing • Generic availability	• 10mg often sufficient • S-enantiomer of citalopram • Less QT concerns than citalopram • Fewer side effects than most SSRIs	• Underdosing in severe depression • Missing early activation syndrome • Overlooking sexual dysfunction • Abrupt	• Take in morning if activating • Sexual side effects common • Full effect takes 2-4 weeks • Don't stop without

		• Good first-line choice	discontinuation • Overlooking emotional blunting	consulting provider • Report any suicidal thoughts
☐ Sertraline	• Mild dopaminergic effects • Fewer drug interactions than most SSRIs • Good anxiolytic properties • Once daily dosing • Generic availability	• Start 25-50mg, titrate weekly • Therapeutic dose: 50-200mg • Take with food (GI effects) • Liquid formulation available • Good choice with polypharmacy	• Underdosing (50mg often insufficient) • Missing GI side effects • Overlooking sexual dysfunction • Abrupt discontinuation • Overlooking diarrhea	• Take with food to reduce GI effects • Sexual side effects common • Full effect takes 2-4 weeks • Higher doses often more effective • Report any suicidal thoughts
☐ Venlafaxine	• Dose-dependent NE effects • Possibly superior efficacy • Multiple formulations • Good anxiolytic properties • Generic availability	• NE effects emerge >150mg daily • XR formulation better tolerated • Monitor BP at higher doses • Significant discontinuation syndrome • Therapeutic dose: 150-225mg	• Underdosing (75mg often insufficient) • Missing BP elevation • Overlooking discontinuation risk • Abrupt discontinuation • Overlooking drug interactions	• Take with food to reduce GI effects • Never stop abruptly • Report dizziness, BP changes • Higher doses often more effective • XR formulation once daily

MEDICATION	UNIQUE ADVANTAGES	CLINICAL PEARLS	COMMON PITFALLS	PATIENT EDUCATION POINTS
☐ Duloxetine	• Balanced 5-HT/NE effects at all doses • FDA-approved for pain conditions • Once daily dosing • Less BP effect than venlafaxine • Generic availability	• Start 30mg, increase after 1 week • Therapeutic dose: 60mg • Enteric-coated (don't crush) • Take consistently with/without food • Less discontinuation effects than venlafaxine	• Underdosing (30mg often insufficient) • Missing hepatic contraindications • Overlooking drug interactions • Abrupt discontinuation • Overlooking GI side effects	• Swallow whole, don't crush or chew • Take consistently with/without food • Report any liver problems • Sexual side effects common • Good for pain conditions

Bupropion	• No sexual dysfunction • Weight neutral/ weight loss • Activating properties • Multiple formulations • Generic availability	• Start low, titrate slowly • XL formulation once daily • Morning dosing to prevent insomnia • Seizure risk dose dependent • Good for fatigue, concentration issues	• Prescribing in seizure disorders • Missing anxiety exacerbation • Overlooking insomnia • Exceeding maximum doses • Overlooking eating disorder history	• Take in morning to prevent insomnia • Different from most antidepressants • No sexual side effects • May help with focus/energy • Don't take late in the day
Amitriptyline	• Potent for pain syndromes • Sedating properties • Once daily dosing • Low cost • Generic availability	• Start low (10-25mg), titrate slowly • Bedtime dosing to utilize sedation • Anticholinergic effects dose dependent • Therapeutic plasma levels: 80-200 ng/mL • ECG monitoring recommended	• Prescribing in elderly • Missing cardiac contraindications • Overlooking anticholinergic effects • Overlooking drug interactions • Overlooking overdose lethality	• Take at bedtime • May cause dry mouth, constipation • Avoid alcohol completely • Report any heart palpitations • Keep away from children (lethal in overdose)
Phenelzine	• Start low (15mg), titrate slowly • BP monitoring required • Multiple drug interactions		• Missing drug interaction warnings • Overlooking orthostatic hypotension • Inadequate BP	regularly • Report severe
• Effective for atypical depression • Effective for treatment-resistant cases • Anxiolytic properties • Social anxiety • Dietary tyramine restrictions essential			• Follow dietary restrictions strictly • Check all medications with provider • Monitor BP	

MEDICATION	UNIQUE ADVANTAGES	CLINICAL PEARLS	COMMON PITFALLS	PATIENT EDUCATION POINTS
	efficacy • Unique mechanism	• 2-week washout before/after other antidepressants • Missing dietary education	monitoring • Overlooking edema	headache immediately • Avoid aged/ fermented foods

Mirtazapine	• Rapid onset of sleep/appetite effects • Minimal sexual dysfunction • Once daily dosing • Minimal drug interactions • Generic availability	• Start 15mg at bedtime • Less sedating at higher doses (receptor profile) • Weight gain monitoring important • Orally disintegrating tablet available • Good for insomnia, anxiety, appetite stimulation	• Missing paradoxical dose-response for sedation • Overlooking weight gain • Underdosing for depression • Overlooking rare blood dyscrasias • Morning dosing	• Take at bedtime • May increase appetite/weight • Less sexual side effects than most • Higher doses less sedating • Report unusual bruising/infection

Switching and Cross-Titration Protocols

FROM	TO SSRI	TO SNRI	TO BUPROPION	TO MIRTAZAPINE
SSRI (Keks et al., 2016)	• Direct switch for most SSRIs • Fluoxetine: taper and wait 2-5 days before starting new SSRI • Start new SSRI at low-moderate dose • Monitor for serotonin syndrome	• Direct switch for most SSRIs • Fluoxetine: taper and wait 2-5 days before starting SNRI • Start SNRI at low dose (venlafaxine 37.5mg, duloxetine 30mg) • Titrate SNRI as tolerated	• Direct switch possible • Start bupropion 150mg daily for 4 days, then increase • Consider overlap for 1-2 weeks if tolerated • Monitor for activation/anxiety	• Direct switch possible • Start mirtazapine 15mg at bedtime • Consider overlap for 1-2 weeks if tolerated • Monitor for excessive sedation
SNRI (Keks et al., 2016)	• Taper SNRI over 2-4 weeks • Start SSRI at low moderate dose when SNRI at 50% dose • Complete SNRI taper as SSRI increased • Monitor for discontinuation symptoms	• Venlafaxine to duloxetine: direct switch possible • Duloxetine to venlafaxine: taper duloxetine by 50%, start venlafaxine 37.5mg • Complete cross titration over 2-4 weeks • Monitor for BP changes	• Taper SNRI over 2-4 weeks • Start bupropion 150mg daily when SNRI at 50% dose • Complete SNRI taper as bupropion increased • Monitor for activation/anxiety	• Taper SNRI over 2-4 weeks • Start mirtazapine 15mg when SNRI at 50% dose • Complete SNRI taper as mirtazapine increased • Monitor for excessive sedation

FROM	TO SSRI	TO SNRI	TO BUPROPION	TO MIRTAZAPINE

Bupropion (Huecker et al., 2024)	• Direct switch possible • Start SSRI at low moderate dose • Consider overlap for 1-2 weeks if tolerated • Monitor for serotonergic effects	• Direct switch possible • Start SNRI at low dose • Consider overlap for 1-2 weeks if tolerated • Monitor for BP changes	—	• Direct switch possible • Start mirtazapine 15mg at bedtime • Consider overlap for 1-2 weeks if tolerated • Monitor for excessive sedation
TCA	• Taper TCA over 2-4 weeks • Start SSRI at low dose when TCA at 50% dose • Complete TCA taper as SSRI increased • Monitor for anticholinergic withdrawal	• Taper TCA over 2-4 weeks • Start SNRI at low dose when TCA at 50% dose • Complete TCA taper as SNRI increased • Monitor for anticholinergic withdrawal	• Taper TCA over 2-4 weeks • Start bupropion 150mg when TCA at 50% dose • Complete TCA taper as bupropion increased • Monitor for seizure threshold	• Taper TCA over 2-4 weeks • Start mirtazapine 15mg when TCA at 50% dose • Complete TCA taper as mirtazapine increased • Monitor for excessive sedation
MAOI	• Discontinue MAOI • Wait 14 days • Start SSRI at low dose • Titrate SSRI as tolerated • Monitor for serotonin syndrome	• Discontinue MAOI • Wait 14 days • Start SNRI at low dose • Titrate SNRI as tolerated • Monitor for serotonin syndrome	• Discontinue MAOI • Wait 14 days • Start bupropion at low dose • Titrate bupropion as tolerated • Monitor for hypertensive reaction	• Discontinue MAOI • Wait 14 days • Start mirtazapine at low dose • Titrate mirtazapine as tolerated • Monitor for serotonin syndrome
Mirtazapine	• Direct switch possible • Start SSRI at low moderate dose • Consider overlap for 1-2 weeks if tolerated • Monitor for serotonergic effects	• Direct switch possible • Start SNRI at low dose • Consider overlap for 1-2 weeks if tolerated • Monitor for BP changes	• Direct switch possible • Start bupropion 150mg daily • Consider overlap for 1-2 weeks if tolerated • Monitor for activation/anxiety	—