UNIVERSITY OF ALBERTA

Managing Adverse Effects

Mental Health Assessment and
Prescribing by Alberta Pharmacists
(MAP-AP) Study Group

REB ID Pro00093776

Learning Objectives

1. Describe patient and therapeutic factors that affect the choice of an an antidepressants
2. Review classes of antidepressants and their common adverse effects
   a. Tricyclic Antidepressants
   b. Monoamine Oxidase Inhibitors
   c. Serotonin Reuptake Inhibitors
   d. Serotonin Norepinephrine Reuptake Inhibitors
   e. Serotonin-2A Antagonists/Reuptake Inhibitors
   f. Norepinephrine Dopamine Reuptake Inhibitors
   g. Serotonin Modulator/Stimulator
3. Describe the approach to managing common adverse effects of antidepressants

Selecting an antidepressant

Patient Factors	Therapeutic Factors
• Patient preference • Age and sex • Severity • Comorbid disorders • Prior response • Family history of response • Sensitivity to side effects • Potential of biomarkers • Cost/availability	• Efficacy/tolerability/safety • Potential for drug-drug interactions • Simplicity of use • Discontinuation Syndrome

Classes of Medication: Antidepressants

Monoamine Oxidase Inhibitor (MAOI)	Phenelzine, tranylcypromine
Norepinephrine Dopamine Reuptake Inhibitors (NDRI)	Bupropion
Noradrenergic Specific Serotonergic Antidepressant (NASSA)	Mirtazapine
Selective Serotonin Reuptake Inhibitors (SSRI)	Citalopram, escitalopram, fluvoxamine, fluoxetine, paroxetine, sertraline
Selective Serotonin Norepinephrine Reuptake Inhibitors (SNRI)	Venlafaxine, duloxetine, desvenlafaxine, levomilnacipran
Serotonin-2A antagonists/reuptake inhibitor (SARI)	Trazodone
Serotonin Modulator/ Stimulator (SMS)	Vortioxetine
SSRI/ serotonin partial agonist	Vilazodone
Tricyclic Antidepressants (TCA)	Secondary amines: desipramine, nortriptyline Tertiary amine: amitriptyline, clomipramine, doxepin, imipramine, trimipramine
Reversible MAO-Inhibitor (RIMA)	Moclobemide

Pharmacology: Antidepressants

Class	Drugs	Re-uptake Inhibition			Receptor Blockade			Potent CYP enzyme *inhibition*		
		SRI	NRI	DRI	Hist	Musc	Alpha1	2D6	2C19	1A2
SSRIs	Fluoxetine	+++	-					√		
	Fluvoxamine	+++	-					√	√	√
	Sertraline	+++	-	+		-	-		√	
	Paroxetine	++++	+	+		++		√		
	Citalopram	++	-					(√) weak		
	Escitalopram	++	-							
TCAs	Amitriptyline	+++	++	-	++	++++	++	√	√	
	Nortriptyline	++	++++	-	+	+	+			
NDRI	Bupropion	-	-	+						
SNRI	Venlafaxine	++	-							
	Duloxetine	++	-							
NaSSA	Mirtazapine				++++	-	-			

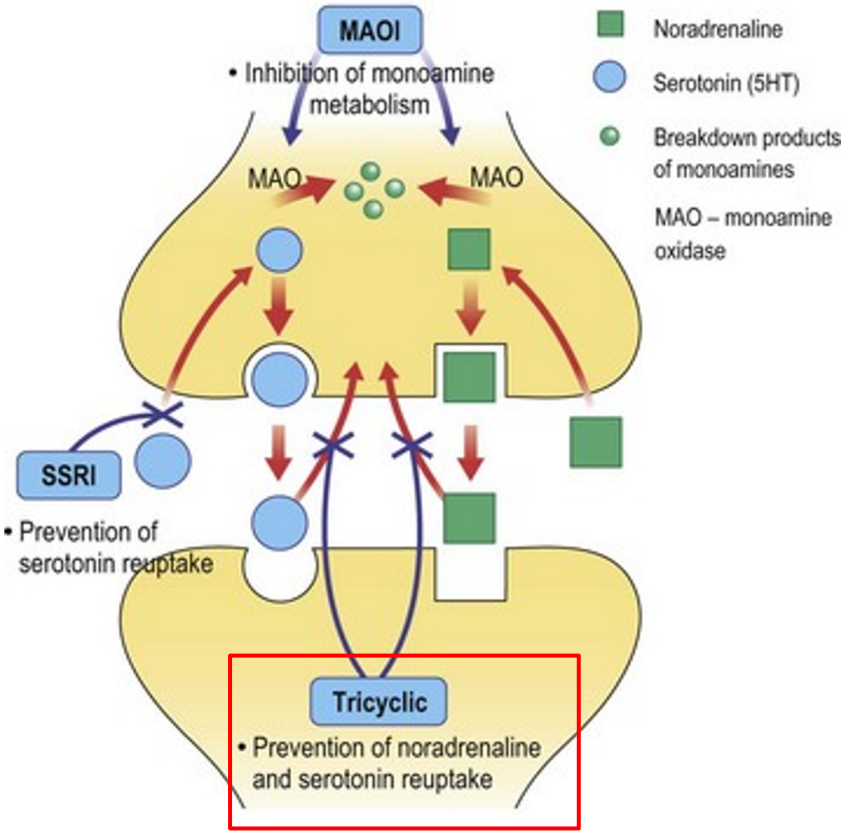
SRI = serotonin reuptake inhibition; **NRI** = norepinephrine reuptake inhibition; **DRI** = dopamine reuptake inhibition
Drug Class: SSRI= selective serotonin reuptake inhibitor; TCA= tricyclic antidepressant; NDRI= norepinephine dopamine reuptake inhibitor; SNRI= serotonin norepinephrine reuptake inhibitor; NaSSA= noradrenergic and specific serotonergic antidepressant
(+) to (++++) = increasing potency; (-) = weak effect; blank = no effect

https://www.psychdb.com/_media/antidepressant_table.png?cache=

Tricyclic Antidepressants (TCA)

Pharmacology

- Increase 5-HT by blocking the 5-HT transporter (SERT) at presynaptic terminal
- Increase NE by blocking NE transporter (NET) at presynaptic terminal
- Block alpha-1 receptors on postsynaptic neurons (block NE effect)



Side effects

- Anticholinergic effects
- Antihistaminergic effects
- Cardiovascular effects

TCA: Adverse effects

CNS/ Psych	Dizziness, sedation, hyperthermia
HEENT	Blurred vision, dry mouth,
CVS	Orthostatic hypotension, arrhythmia
GI/LIVER	Constipation
GU/RENAL	Urinary retention
MSK	Motor incoordination
ENDO	Weight gain

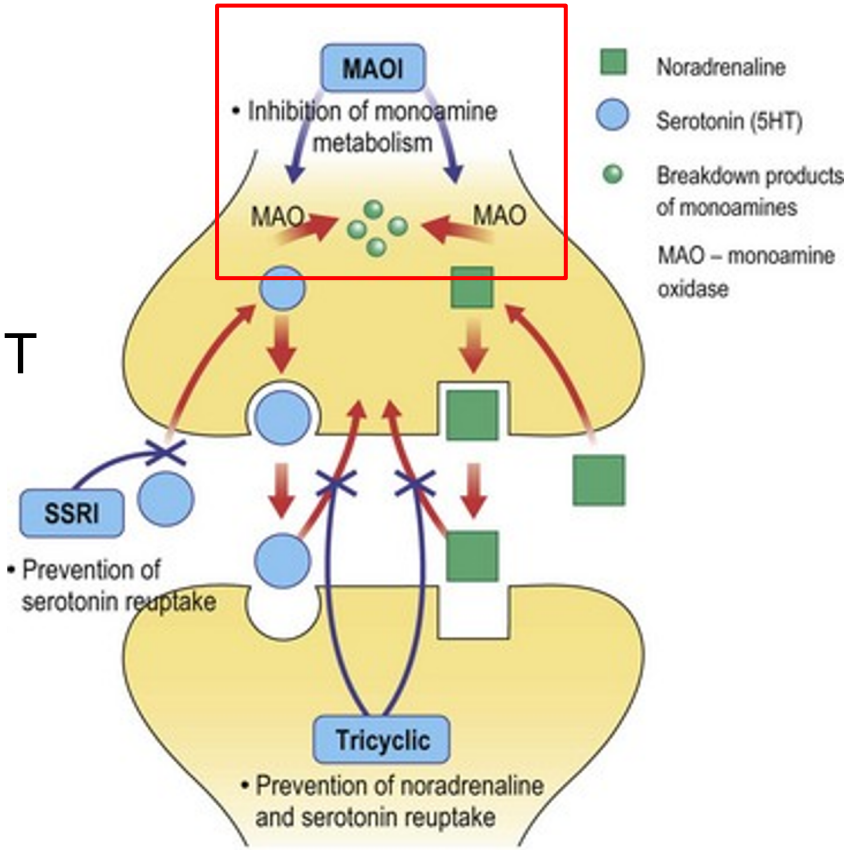
Monoamine Oxidase Inhibitors (MAOI)

Pharmacology

- Irreversible, non-selective (MAO-A and MAO-B) receptor inhibitors
- RIMA: reversible, MAO-A selective inhibitors
- Inhibit the breakdown of NE and 5-HT

Side effects

- Can cause hypertensive crisis if dietary restrictions are not followed



Hypertensive Crisis

- A hypertensive crisis is a severe increase in blood pressure (SBP ≥180)

- Avoid taking the following with MAOI:
  - Cured meat/poultry/fish (e.g. salami)
  - Ages cheeses
  - Concentrated soy products
  - Tap beer
  - Banana Peels
  - Broad beans pods/fava beans
  - Sauerkraut
  - Yeast Extracts

MAOI: Adverse effects

CNS/ PSYCH	Dizziness, sedation, headache, anxiety
HEENT	Blurred vision, dry mouth
CVS	Orthostatic hypotension, edema, hypertension crisis, palpitations
GI/LIVER	Constipation, diarrhea, increased liver transaminase, jaundice
MSK	Tremor

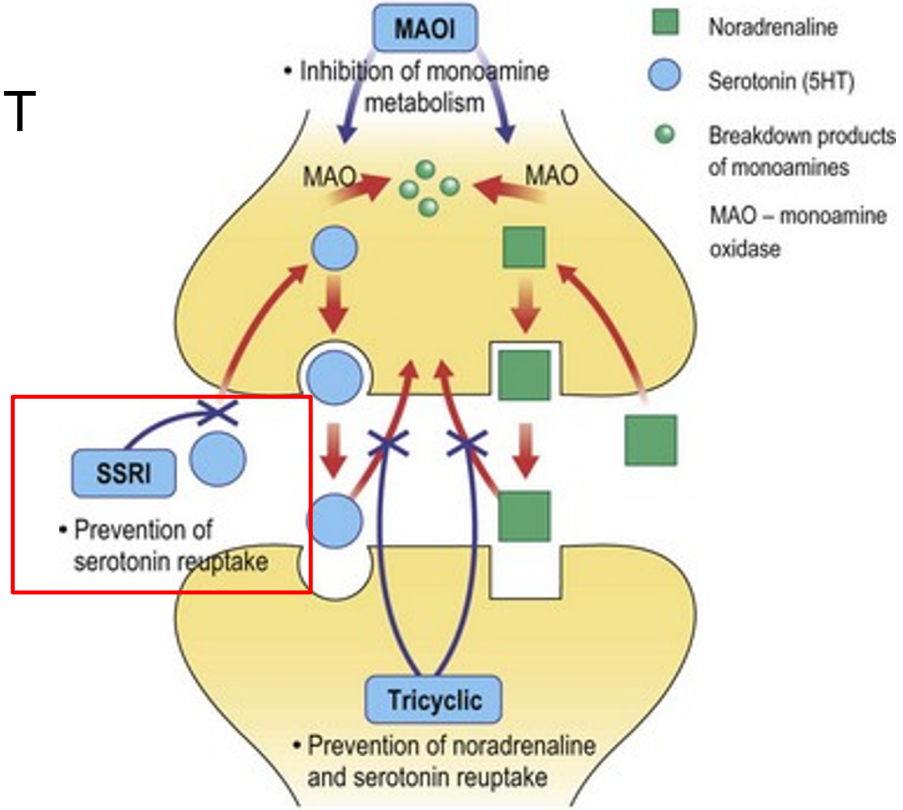
Selective Serotonin Reuptake Inhibitors (SSRI)

Pharmacology

- Increase 5-HT by blocking the 5-HT transporter (SERT) at presynaptic terminal

Side effects

- Serotonin syndrome
- Fewer anticholinergic effects (except paroxetine)
- Potential increase in suicidal thoughts
- Potential increase in GI bleeding



Serotonin Syndrome

- Also known as serotonin toxicity (Varying levels of severity; mild to fatal)
- A potentially life-threatening condition associated with increased serotonergic activity in the CNS
- Rare but can occur with any antidepressant with whose mechanism of action includes increasing serotonin (e.g., high doses, drug overdose, drug interactions)
- Other drugs/herbals that could contribute Serotonin syndrome: St. John's Wort, meperidine, tramadol, fentanyl, dextromethorphan, triptans, and linezolid

Clinical Presentation: Serotonin Syndrome

Clinical Presentation	
CNS/ Psych	Anxiety, agitated delirium, restlessness, disorientation, hyperthermia
HEENT	Dilated pupils, slow/ horizontal eye movements
CVS	Tachycardia
GI/LIVER	Vomiting, diarrhea
MSK	Tremor, hyperreflexia, myoclonus, akathisia
DERM	Diaphoresis

How to manage: Serotonin syndrome

- Can potentially occur with any antidepressant with whose mechanism of action includes increasing serotonin
- Referral to ER: most cases resolve in 24 hours once offending drug(s) are discontinued
  - Delirium can remain for several days
  - Supportive Care, can use benzodiazepines, cyproheptadine

- Varying levels of severity; mild to fatal
- Rare but occurs most often when serotonergic drugs are used in combination at high doses, due to drug interaction or due to overdose
- Other drugs/herbals that could contribute are St Johns Wort, meperidine, tramadol, fentanyl, dextromethmorphan, triptans and linezolid

SSRI: Adverse effects

CNS/ Psych	Dizziness, insomnia, headache, dizziness, anxiety (will subside), increase in suicidal thoughts, serotonin syndrome
HEENT	Teeth grinding (bruxism)
CVS	Orthostatic hypotension, arrhythmia
GI/LIVER	GI bleeding
GU/RENAL	Urinary retention
ENDO/ Sexual	Sexual dysfunction (30%), weight gain

Selective Serotonin Norepinephrine Reuptake Inhibitors (SNRI)

Pharmacology

- Non-selective 5-HT and NE uptake inhibitors; generally similar to TCAs but lack major receptor-blocking actions, resulting in fewer adverse effects
- Venlafaxine: 5-HT blocker at low dose, NE effects at high doses (>150mg)
- Levomilnacipran: most adrenergically active of the SNRI class; more NE activity at lower doses. No CYP inhibition but CYP3A4 substrate.

Side effects

- Similar to SSRI
- Desvenlafaxine: leaves a shell in feces (warn patients)
- Levomilnacipran ER: dose related adverse effects (urinary hesitation, erectile dysfunction)

SNRI: Adverse effects

CNS/ Psych	Dizziness, insomnia, headache dizziness, anxiety, serotonin syndrome
HEENT	Dry mouth
CVS	Tachycardia
GI/LIVER	Nausea, vomiting
GU/RENAL	Urinary retention
ENDO/ Sexual	Sexual dysfunction (30%), weight loss
MSK	Tremor

Serotonin-2A antagonist/ reuptake inhibitor (SARI)

- Trazodone
- Pharmacology
  - Blocks 5HT-2A and 5HT-2C receptors
- Useful for insomnia (up to 100mg/daily); antidepressant doses are much higher (up to 600 mg/daily); food delays absorption so take on an empty stomach if used for sedation

- Adverse effects
  - Orthostatic Hypotension
  - Sedation
  - Priapism
    - Priapism (prolonged erection for 4+ hours) occurs in 1/1000 to 1/10,000 men

SARI: Adverse effects

CNS/ Psych	Dizziness, drowsiness, fatigue, headache, anxiety, increase in suicidal thoughts
HEENT	Dry mouth/ sialorrhea
CVS	Chest pain, hypotension, tachycardia
GI/LIVER	Flatulence, constipation/ diarrhea
GU/RENAL	Urinary frequency/ hesitation
ENDO/ Sexual	Increased libido, change in menstrual flow, weight gain/ weight loss

Norepinephrine Dopamine Reuptake Inhibitors (NDRI)

- Bupropion
- Pharmacology
  - Noradrenaline and dopamine uptake inhibitor
  - Nicotinic ACh receptor antagonist: helpful in smoking cessation
- Lowers seizure threshold, higher risk at doses ≥450 mg

- Adverse effects
  - Side effects similar to SSRIs
  - Minimal weight gain/ sexual dysfunction

NDRI: Adverse effects

CNS/ Psych	Agitation, dizziness, headache, insomnia, migraine
HEENT	Dry mouth, blurred vision
CVS	Tachycardia
RESP	Nasopharyngitis, pharyngitis, rhinitis
GI/LIVER	Constipation, nausea, vomiting
GU/RENAL	Urinary retention
ENDO/ Sexual	Weight loss
DERM	Sweating

Noradrenergic Specific Serotonergic Antidepressant (NASSA)

- Mirtazapine
- Pharmacology
  - Blocks alpha-2 adrenoreceptors and 5-HT-2C receptors to enhance NE and 5-HT release
- At higher doses, more norepinephrine effect; thus, more sedating at lower doses

- Adverse effects
  - Prominent antihistaminergic side effects
  - Virtually no anticholinergic, serotonergic, norepinephrine side effects

NASSA: Adverse effects

CNS/ Psych	Drowsiness, sedation, abnormal dreams, dizziness
HEENT	Dry mouth, blurred vision
CVS	Edema, hypertension, peripheral edema
GI/LIVER	Constipation
GU/RENAL	Urinary retention
ENDO/ Sexual	Increased cholesterol, significant weight gain
DERM	Pruritus

Serotonin Modulator/Stimulator (SMS)

- Vortioxetine
- Pharmacology
  - Inhibits reuptake of serotonin; agonist activity at 5-HT-1A and antagonist activity at 5-HT3 receptors
- Long half life (comparable to fluoxetine); consider implications in breast feeding

- Adverse effects
  - Side effects profile comparable to SSRIs
  - No significant effect on body weight, heart rate, blood pressure
  - Low rates of sedation and insomnia

SMS: Adverse effects

CNS/ Psych	Abnormal dreams, dizziness
HEENT	Dry mouth
CVS	Flushing
GI/LIVER	Nausea, constipation, diarrhea, flatulence
ENDO/ Sexual	Female sexual disorder, male sexual disorder
DERM	Pruritus

SSRI/ Serotonin Partial Agonist

- Vilazodone
- Pharmacology
  - Inhibits CNS neuron serotonin uptake; minimal or no effect on reuptake of NE or dopamine
- Take with food to increase bioavailability

- Adverse effects
  - Side effects profile comparable to SSRIs
  - Low rates of weight gain (0.15-0.59 kg) and sexual dysfunction

SSRI/ Serotonin Partial Agonist: Adverse effects

CNS/ Psych	Headache, dizziness, insomnia, abnormal dreams, restlessness
HEENT	Dry mouth, blurred vision
CVS	Palpitations
GI/LIVER	Diarrhea, nausea, abdominal pain
ENDO/ Sexual	Decreased libido, weight gain
DERM	Night sweats, sweating

Managing common adverse effects of antidepressants

- Will cover the following common adverse effects

CNS/ Psych	Dizziness, Hyperthermia, Sleep disturbance, Serotonin Syndrome
HEENT	Blurred vision, Dry mouth
CVS	Hypotension, QT prolongation
GI/LIVER	Nausea, Diarrhea, Constipation
GU/RENAL	Urinary retention
ENDO/ Sexual	Sexual dysfunction, Weight gain

How to manage: Dizziness

- Mild symptoms may attenuate over several weeks
- Dose adjustment or medication switch

- If due to orthostatic hypotension→ getting up slowly from a sitting or lying position
  - “Dangle” feet when getting out of bed
- If most dizziness occurs after taking medication→ taking pills at night before bed
- Avoid driving or operating heavy machinery
- Encourage adequate fluid intake & avoid excessive salt restriction

How to Manage: Hyperthermia

- Dose adjustment or switch medications
- Keep well hydrated
- Avoid physical activity outside during hot weather or in the middle of the day

How to manage: Sleep Disturbance

- Patients may experience insomnia or sedation/somnolence especially in the early therapy
  - Should improve after 1-2 weeks

- Dose adjustment (↓), adjust timing of dose, or switch medications

- Antidepressants most likely to cause **sedation**: mirtazapine (low dose), trazodone, fluvoxamine and TCAs

- Antidepressants most likely to cause i**nsomnia/anxiety**: bupropion, most SSRIs (especially fluoxetine) and SNRIs

How to manage: Serotonin syndrome

- Referral to ER: most cases resolve in 24 hours once offending drug(s) are discontinued
  - Delirium can remain for several days
  - Supportive Care, can use benzodiazepines, cyproheptadine

Clinical Presentation	
CNS/ Psych	Anxiety, agitated delirium, restlessness, disorientation, hyperthermia
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MSK	Tremor, hyperreflexia, myoclonus, akathisia
DERM	Diaphoresis

How to manage: Blurred vision

- Dose adjustment or medication switch
- If blurred vision is caused by dry eyes→ try eye drops
- Referral to optometrist: can precipitate acute narrow angle glaucoma

How to manage: Dry Mouth

- Dose adjustment or switching medications

- Drinking more water
- Using Oral Balance gel or Biotene mouthwash (or other alcohol free mouthwash)
- Sucking on sour candies or ice
- Prescribing or suggesting pilocarpine drops

How to manage: QT prolongation

- QTc > 450 ms (♂) or >460 ms (♀) begin to assess risk factors, increase vigilance.
- If QTc > 500 ms – change in therapy is prudent
- Assess risk factors:
  - Atrial Fibrillation
  - Old age
  - Female sex
  - Electrolyte imbalances
  - Congenital Long QT interval
  - Concomitant medications that increase QT interval (e.g., antiarrhythmics, antidepressants, antimicrobials, methadone, etc.)
  - Underlying heart disease
  - Recent MI

How to manage: QT prolongation

- Educate patient to contact provider immediately if dizziness, palpitations or syncope occur

- If a patient is on antidepressant with higher QT risk:
  - Consider ECG
  - Baseline periodic electrolyte monitoring (K+, MG+)
  - Initiate electrolyte supplementation, if warranted

- Carefully evaluate new Rxs for additional QT prolongation potential

How to manage: Nausea & Diarrhea

Nausea

- Nausea generally decreases over time
  - Related to serotonin
  - Desensitization of serotonin receptors take ~ 1-2 weeks
- Taking pills with food may minimize nausea

Diarrhea

- Diarrhea usually dose related and transient

How to manage: Constipation

- Dose adjustment or medication switch

- Drink more water
- Consume more fruits/vegetables or use a fibre supplement
- Exercise
- Use an OTC product to relieve constipation

How to Manage: Urinary retention

- Due to anticholinergic effects
- Dose adjustment or switch medications
- After dose adjustment, assess any other underlying causes of urinary retention (e.g., BPH)

How to manage: Sexual Dysfunction

- Sexual dysfunction usually does not improve with time
- Dose-related, reversible; affect both genders
- SSRI are worse than SNRIs
  - Paroxetine = highest risk SSRI
  - Fluvoxamine = least risk of SSRI

- If bothersome, switch medications
  - Lower risk: moclobemide, bupropion and mirtazapine

- Refer to Clinical Handbook for other options such as buspirone, cyproheptadine, yohimbine, dextroamphetamine, mirtazapine, etc.

How to manage: Sexual Dysfunction

- Decreased libido, importance, or ejaculatory disturbance
  - Sildenafil 25-100 mg PRN

- Anorgasmia/delayed orgasm
  - Switch to bupropion 75-300 mg/day

How to manage: Weight gain

- If bothersome, switch medications
  - Mirtazapine is associated with the most weight gain (26% of patients gaining at least 7% of their body weight)
  - Mirtazapine > SSRIs > SNRIs

- Difference between SSRIs do exist
  - Paroxetine is associated with highest weight gain and fluoxetine is the least
- Bupropion does not have a significant impact of weigh

Summary

- While side effects from antidepressants are common, they can be managed by pharmacist intervention
- Side effects are similar within the same class of medications
- If side effects are intolerable for a patient, switching to another class of antidepressants is a reasonable option
- May have to encourage a patient to stick with their antidepressants
  - Often side effects subside with time
  - Take at least 2-4 weeks to see benefits

Summary: Adverse Effects

Table 7. Prevalence of Adverse Events among Newer Antidepressants: Unadjusted Frequency (%) of Common Adverse Events as Reported in Product Monographs.

	Nausea	Constipation	Diarrhea	Dry Mouth	Headaches	Dizziness	Somnolence	Nervousness	Anxiety	Agitation	Insomnia	Fatigue	Sweating	Asthenia	Tremor	Anorexia	Increased Appetite	Weight Gain	Male Sexual Dysfunction
Citalopram	21		8	19				3	3	2		5	11		8	4			9
Escitalopram	15	4	8	7	3	6	4	2	2		8	5	3		2		2	2	10
Fluoxetine	21			10			13	14	12		16		8	9	10	11			2
Fluvoxamine	37	18	6	26	22	15	26	2	2	16	14		11	5	11	15			1
Paroxetine	26	14	11	18	18	13	23	5	5	2	13		11	15	8		1		16
Sertraline[a]	26	8	18	16	20	12	13	3	3	6	16	11	8		11	3	1		16
Desvenlafaxine[b]	22	9		11		13	4	<1	3		9	7	10		2				6
Duloxetine	20	11	8	15		8	7		3		11	8	6		3				10
Levomilnacipran	17	9		10	17	8			2		6		9						11
Milnacipran	12	7		9	10				4		7	3	4		3				
Venlafaxine IR	37	15	8	22	25	19	23	13	6	2	18		12	12	5	11			18
Venlafaxine XR	31	8	8	12	26	20	17	10	2	3	17		14	8	5	8			16
Agomelatine[c]	C	C	C		C	C	C		C		C	C	C						
Bupropion SR[d]	11	7	4	13	28	7	3	5	5	2	8		2	2	3				
Bupropion XL	13	9		26	34	6			5	2	16				3				
Mirtazapine		13		25		7	54							8	7		17	12	
Moclobemide	5	4	2	9	8	5	4	4	3	5	7	3	2	1	5				
Vilazodone[e]	24		29	7	14	8	5				6	3					3	2	5
Vortioxetine[f]	23	4	5	6		5	3				3	3	2						<1

When data from multiple doses were reported separately, the data from the minimum therapeutic dose were used (indicated by footnotes). Data sources and references are available in Supplemental Table S3. Clear cells represent 0% to 9%; shaded cells, 10% to 29%; and black cells, 30% and higher.

[a]Data from all indications.

[b]Data from 50-mg dose.

[c]C, common effects, ≥1% and <10%.

[d]Data from 100- to 150-mg dose.

[e]Data from 40-mg dose.

[f]Data from 10-mg dose.

References