ALL I WANT FOR THE HOLIDAYS IS MORE SEROTONIN:

INDIVIDUALIZING ANTIDEPRESSANT THERAPY

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CSHP virtual Event Nov 30, 2021

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HOUSEKEEPING

- Zoom polls
- Disclosure:
  - I have no current or past relationships with commercial entities
  - I have received a speaker's fee (gift card) from CSHP-AB Branch for this learning activity
  - This program has received no financial or in-kind support from any commercial or other organization (other than speaker's fee from CSHP-AB Branch)

REFLECTIVE QUESTIONS

- What is your current comfort level in choosing an antidepressant for your patients with major depressive disorder?

  1 - Very uncomfortable. what is an antidepressant? Really don't know what I'm doing

  2 –Mostly Uncomfortable

  3 – Somewhat comfortable. Can figure out an antidepressant choice but requires guidance

  4 – Mostly comfortable – Can think of an Antidepressant but need to chat it over with a pro

  5- Very comfortable. I'm a pro.

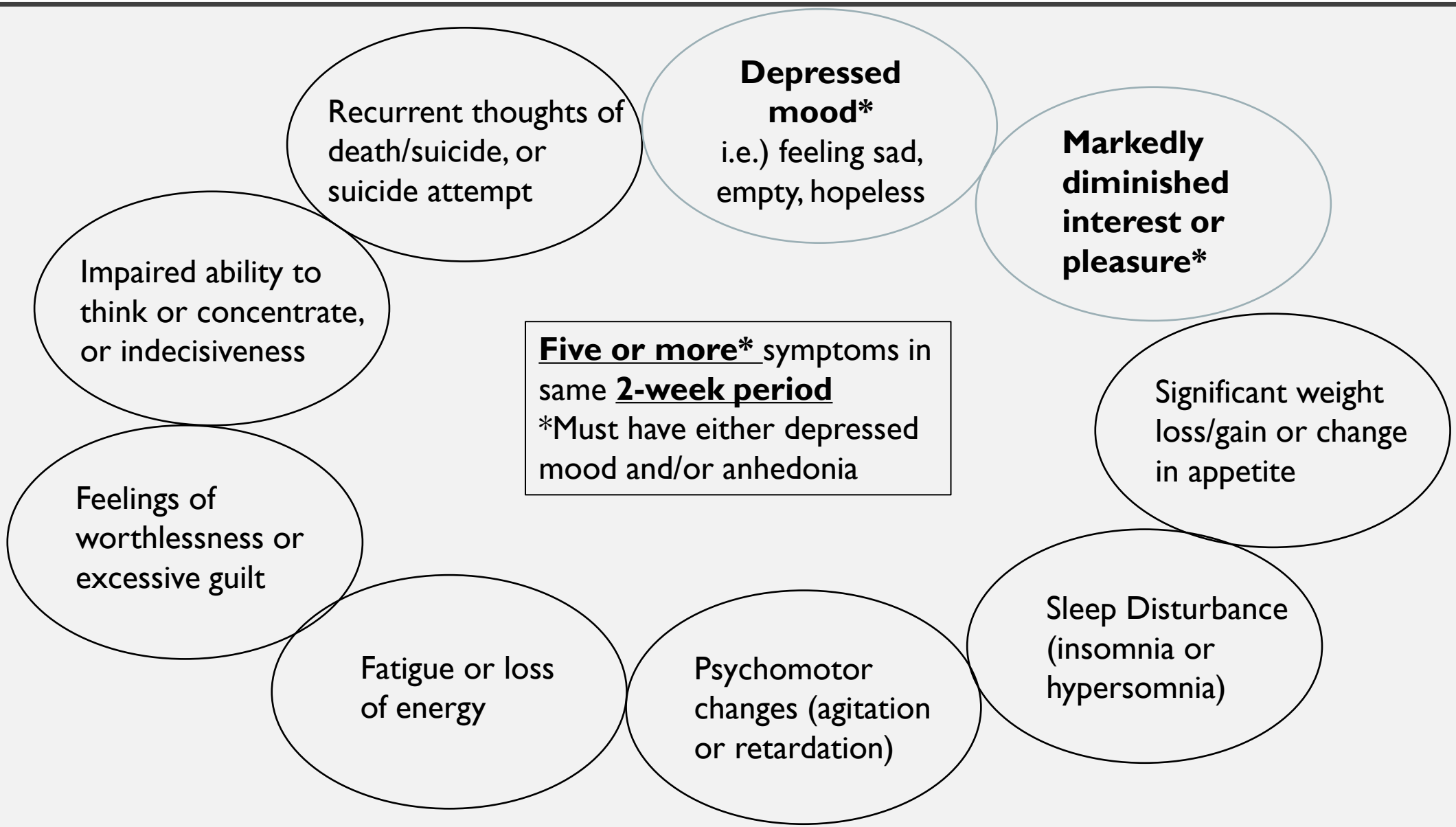
- Reflecting on the above question, what are some factors that make choosing or adjusting an antidepressants uncomfortable or less comfortable?
  - *If you feel comfortable please type answer in zoom chat box*

LEARNING OBJECTIVES

By the end of this presentation:

1) Describe common Depression assessment instruments and use of these instruments in practice
2) Summarize most recent treatment guidelines alongside pragmatic and network meta-analysis data of unipolar depression treatment with antidepressants
3) Establish a role of individualized antidepressant therapy based on shared decision making with patients
4) Propose a preliminary pilot algorithm to assist with individualizing antidepressant therapy

MAJOR DEPRESSIVE DISORDER (MDD) DSM 5



Lam 2016

DEPRESSION ASSESSMENT INSTRUMENTS

Outcome	Clinician-Rated	Patient-Rated
Symptoms	• Hamilton Depression Rating Scale (HAM-D) • Montgomery-Asberg Depression Rating Scale (MADRS) • Inventory for Depressive Symptomatology (IDS)	• **Patient Health Questionnaire (PHQ-9)** • Quick Inventory for Depressive symptomatology, self Rated (QIDS-SR) • Clinically Useful Depression Outcome Scale (CUDOS) • **Beck's Depression Inventory (BDI)**
Functioning	• Multidimensional Scale of Independent Functioning (MSIF) • WHO Disability Assessment Scale (WHO-DAS) • Social and Occupational Functioning Assessment Scale (SOFAS)	• Sheehan Disability Scale (SDS) • WHO-DAS, self rated • Lam Employment Absence and Productivity Scale (LEAPS)
Side Effects	UKU Side Effect Rating Scale	Frequency, Intensity and Burden of Side Effects Rating (FIBSER)
Quality of Life	Quality of Life Interview (QOLI)	• Quality of Life, Enjoyment and Satisfaction Questionnaire (QLESQ) • EuroQoL-SD (EQ-5D)

Lam 2016

PHQ-9

Over the last **2 weeks**, how often have you been bothered by any of the following problems?				
	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself—or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed? Or the opposite—being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead or of hurting yourself in some way	0	1	2	3
Total score =		+	+	+

Score interpretation	5-9 =Mild	10-14=Moderate	15 – 19 Moderately Severe	20 – 27 Severe

If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?	Not difficult at all	Somewhat difficult	Very difficult	Extremely difficult

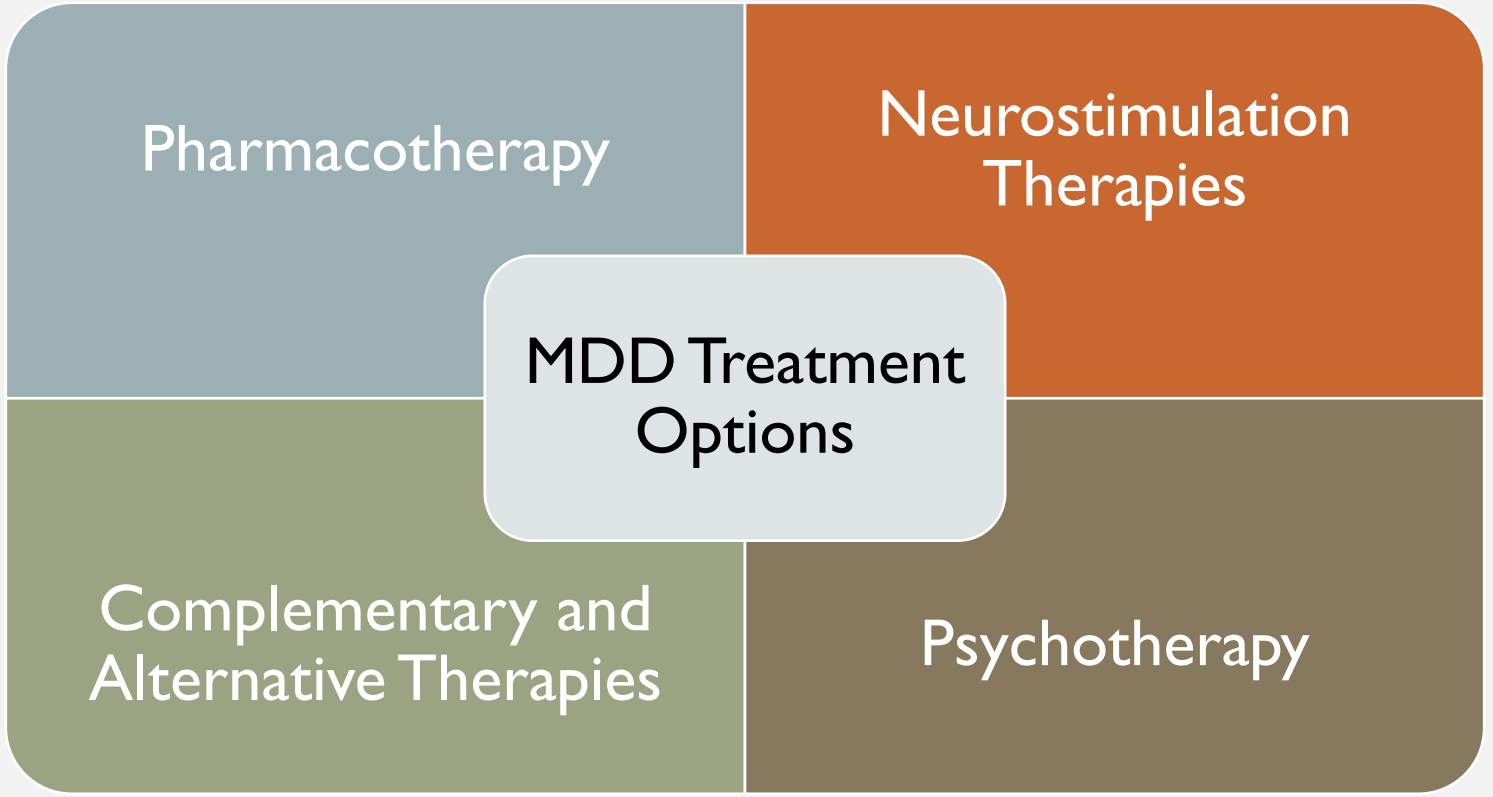
Kroenke, 2001

GOALS OF DEPRESSION TREATMENT

Phase	Duration	Goals	Activities
Acute	8-12 weeks	Remission of symptoms Restoration of functioning	• Establish therapeutic alliance • Educate and support self-management • Select and deliver evidence-based treatment(s) • Monitor progress
Maintenance	6-24 months, or longer	Return to full functioning and quality of life Prevention of recurrence	• Educate and support self-management • Rehabilitate • Treat comorbidities • Monitor for recurrence

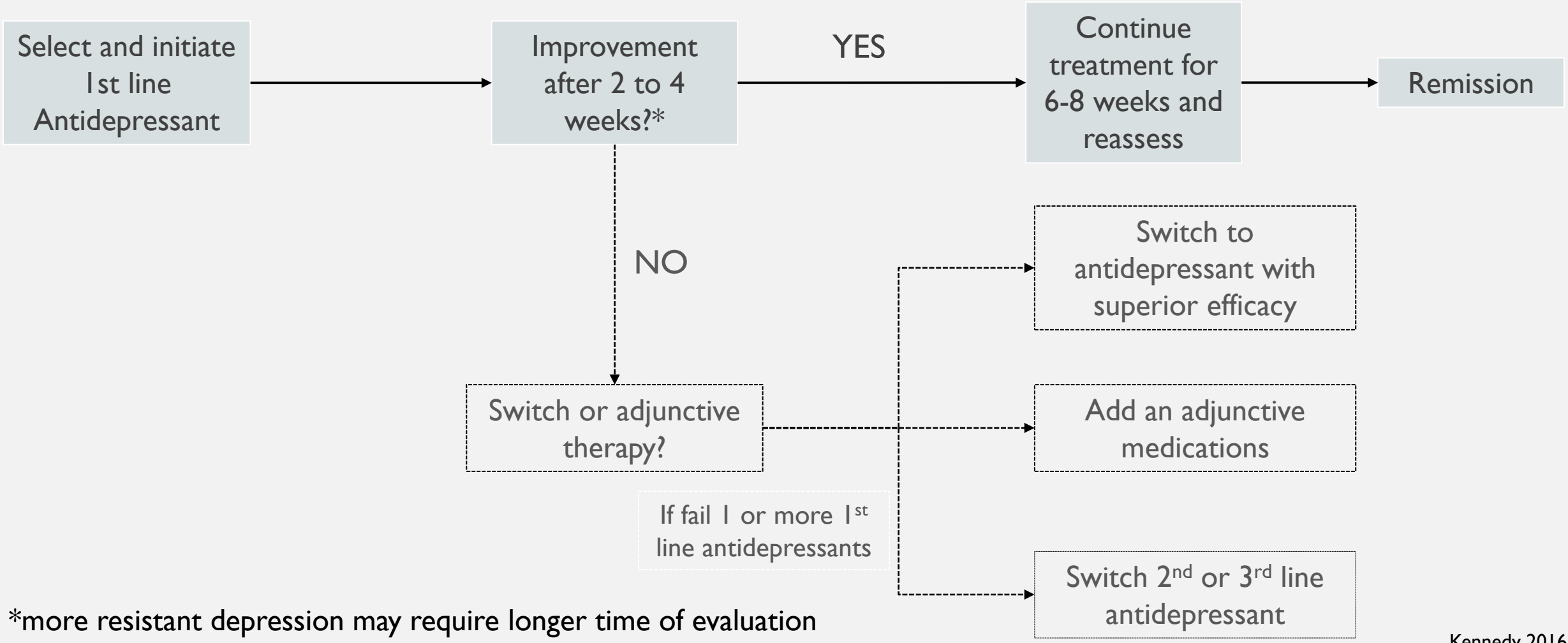
Lam 2016

CANMAT 2016 DEPRESSION GUIDELINES



Kennedy 2016

CANMAT DEPRESSION GUIDELINES: PHARMACOTHERAPY TREATMENT ALGORITHM



*more resistant depression may require longer time of evaluation

Kennedy 2016

CANMAT DEPRESSION GUIDELINES: PHARMACOTHERAPY TREATMENT

First-Line (Level I evidence)		
Class	**Agent**	**Daily Dose**
SSRI	Citalopram	20–40 mg
	Escitalopram	10–20 mg
	Fluoxetine	20–60 mg
	Fluvoxamine	100–300 mg
	Paroxetine	IR: 20–50 mg CR: 25 – 62.5mg
	Sertraline	50–200 mg
SNRI	Desvenlafaxine	50–100 mg
	Duloxetine	60 mg
	Venlafaxine	75–225 mg
NDRI	Bupropion	150–300 mg
Other	Mirtazapine	15–45 mg
	Vortioxetine	10–20 mg
Not available in Canada	~~Agomelatine~~	~~25–50 mg~~
	~~Mianserin~~	~~60–120 mg~~
	~~Milnacipran~~	~~100 mg~~

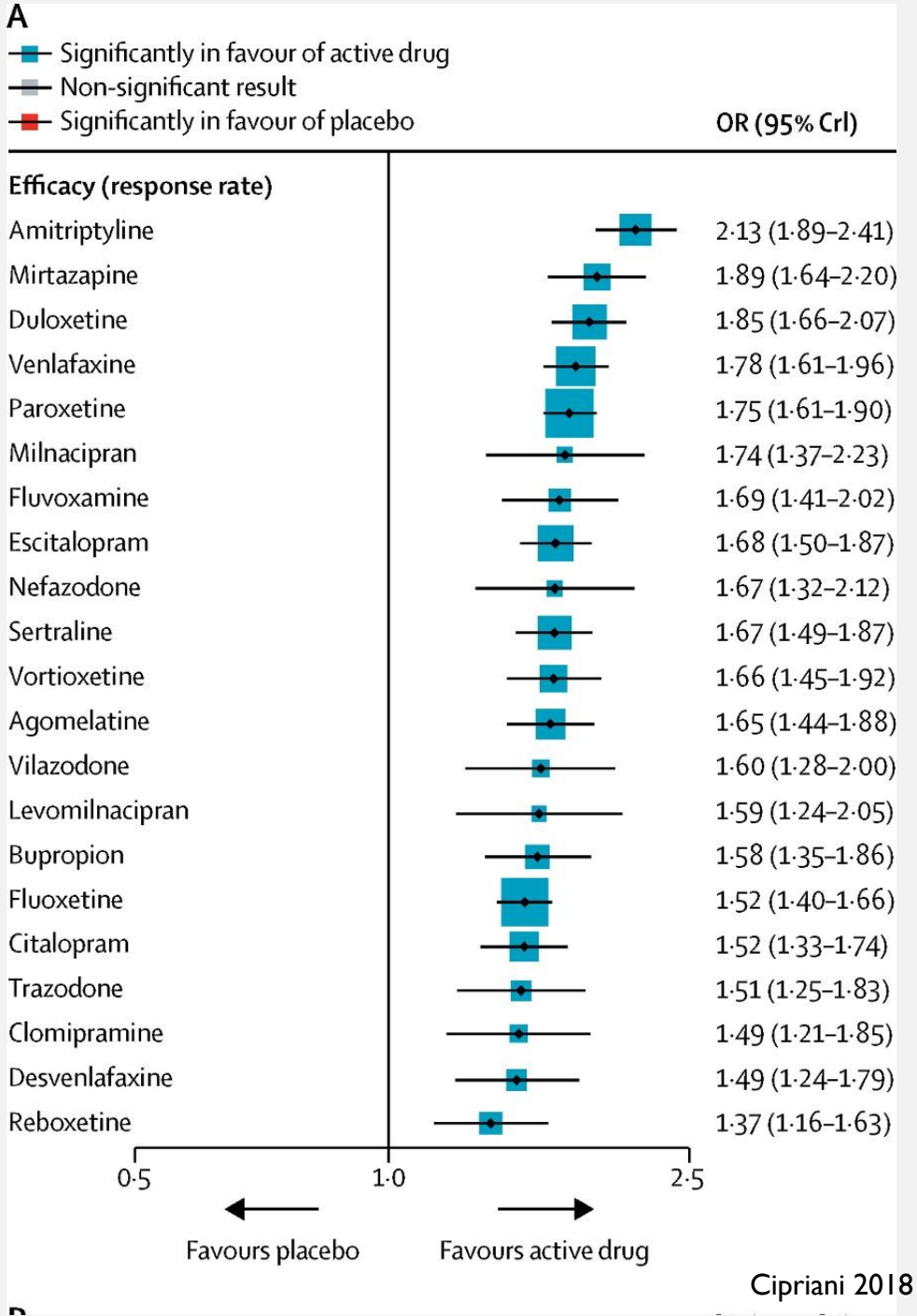
Kennedy 2016

CIPRIANI ET AL, 2018: NETWORK META-ANALYSIS

Trial	522 double-blind, parallel, published and unpublished RCTs between 1979 and 2016	
P	**Acute treatment of adults** of unipolar major depressive disorder Baseline: Mean age 44 years/ 62% Women Moderate to Severe depression (mean HAMD-17 = 25.3 (severe) in 89% studies	
I	21 antidepressants ; Median trial duration 8 weeks (4-12 weeks)	
C	Clomipramine, amitriptyline, placebo and each other	
O	**Primary Efficacy** (response rate measured by the total number of patients who had a reduction of ≥50% of the total score on a standardised observer-rating scale for depression) **Acceptability** (treatment discontinuation measured by the proportion of patients who withdrew for any reason) Secondary outcome: • Endpoint depression score	
Limitations and Comments	• Overall quality of data not great • Various scales of efficacy	• 78% funded by industry

EFFICACY

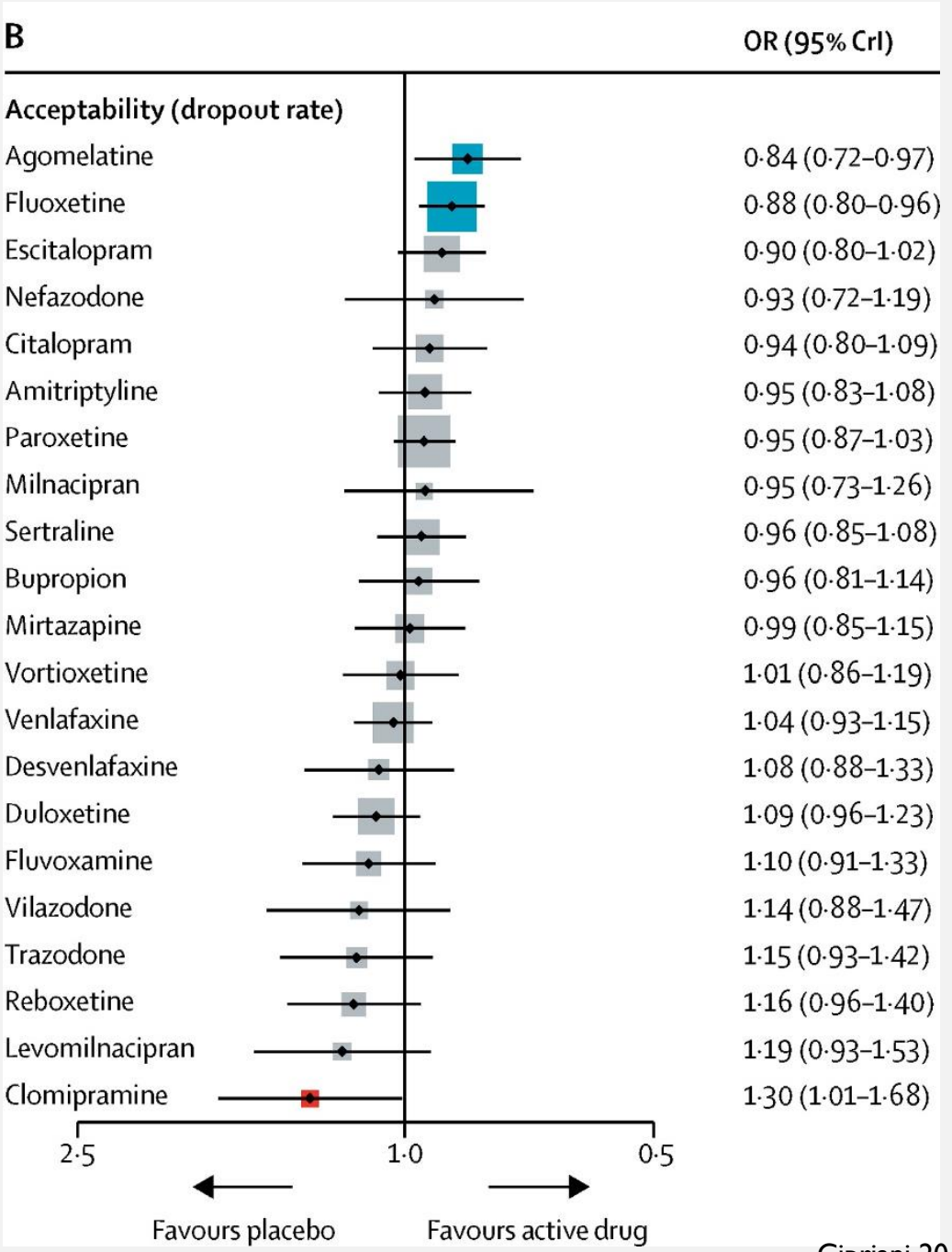
First-line Antidepressant	Response OR (95%CrI)	NNT
paroxetine	1.75 (1.61-1.90)	4
fluvoxamine	1.69 (1.41-2.02)	5
escitalopram	1.68 (1.50-1.87)	5
sertraline	1.67 (1.49-1.87)	5
citalopram	1.52 (1.33-1.74)	7
fluoxetine	1.52 (1.40-1.66)	7
duloxetine	1.85 (1.66-2.07)	4
venlafaxine	1.78 (1.61-1.96)	4
desvenlafaxine	1.49 (1.24-1.79)	7
bupropion	1.58 (1.35-1.86)	6
mirtazapine	1.89 (1.64-2.20)	3
vortioxetine	1.66 (1.45-1.92)	5



Cipriani 2018

ACCEPTABILITY

First-line Antidepressant	Drop out OR (95%CrI)	NNH
paroxetine	0.95 (0.87-1.03)	-
fluvoxamine	1.10 (0.01-1.33)	-
escitalopram	0.90 (0.80-1.02)	-
sertraline	0.96 (0.85-1.08)	-
citalopram	0.94 (0.80-1.09)	-
fluoxetine	**0.88 (0.80-0.96)**	**43**
duloxetine	1.09 (0.96-1.23)	-
venlafaxine	1.04 (0.93-1.15)	-
desvenlafaxine	1.08 (0.88-1.33)	-
bupropion	0.96 (0.81-1.14)	-
mirtazapine	0.99 (0.85-1.15)	-
vortioxetine	1.01 (0.86-1.19)	-



Cipriani 2018

LEWIS ET AL, 2019 – PRAGMATIC RCT

Trial	**PANDA trial -** RCT, double-blind, multicenter (England)
P	• GP uncertain of antidepressant benefit (diagnostic uncertainty) • Adult patients agreeable to try antidepressant Baseline (n=653): • mean age: 39.7 years/ 59% female/ 66% employed/ 69% 'A-level or higher' • 54% MDD/ 46% GAD → 30% MDD+GAD • CIS-R 20-49: 351(54%) severe symptoms
I	Sertraline 50 to 150mg daily, 12 weeks duration
C	Placebo
O	**Primary Outcome: PHQ-9 total score difference in 6 weeks**: 0·96 (0·86 to 1·07) p=0.11 Secondary Outcomes: • PHQ-9 total score differences @12 weeks: 0·87 (95% CI 0·79 to 0·97)* • GAD-7 total score differences: 0·83 (0·75 to 0·91) p <0·0001* and improved overtime (p=0.0075) • SF-12 mental health QoL differences: 2·41 (1·14 to 3·69) p =0·0002* and no difference over time • Self-reported improvement difference: 1·96 (1·45–2·63) p <0·0001* and no difference over time
Limitations and Comments	• 99 (15%) patients did not meet depression or anxiety criteria • % mild depression patients (PHQ-9 <10): Sertraline 114 (43%) vs PBO 101(36%) • not powered to study effect of severity and duration of symptoms on outcomes

KATO ET AL, 2021: NETWORK META-ANALYSIS

Trial	40 trials - Double Blind, Placebo-controlled monotherapy RCTs with duration of ≥ 12 weeks
P	Adult unipolar major depressive disorder who were stable and responded to active drug 'enrichment design' studies only
I	31 Antidepressants
C	Placebo
O	**Primary Outcome: Overall Difference in Relapse Rate** • AD 20.9% vs. PBO 39.7% RD=0.19 (95%CI 0.16–0.22, p< 0.00001) **ARR: 0.188 NNT=6** **Subgroup:** • Difference in Relapse rates and study duration: 6-months (mean 25 weeks) diff= 18.0% (OR 0.41, p< 0.00001) 1 year (mean 56 weeks) diff= 19.9% (OR 0.35, p< 0.00001) • Difference in Relapse Rate and duration of continuous treatment AFTER remission: 1 month (mean 0.2 weeks) diff = 19.1% (OR 0.38, p< 0.00001) > 6 months (mean 27 weeks) Diff= 17.5% (OR 0.40, p< 0.00001)
Limitations and Comments	I^2= 38 to 51% (moderate heterogeneity) Did not look at whether or not severity correlates with relapse rate Varying scales and definition of relapse in studies

PLACEBO EFFECT

- 35-40% mean Placebo response rate in Antidepressant trials
  - Stable over 25 years of antidepressant trials
  - Large variability in effect (0 to 70%) in 252 studies
- 25% mean placebo drop-out rate in Antidepressants trials
- Lower Response Rate (Risk Ratio 0.87; 95% CI 0.83, 0.92) and higher all-cause dropout rate (1.19; 1.08, 1.31) in Placebo-Controlled vs Head-to-Head trials for same antidepressant

Fukrukawa 2016
Li 2019
Salatani 2018

BOTTOM LINE FROM MOST RECENT EVIDENCE

- Most if not all studies included were poorly executed, biased, based on outcomes of questionable clinical relevance
- Moderate to Severe MDD:
  - Acute treatment: Antidepressants reduce ≥50% depressive symptoms (NNT 4-7)
  - Relapse data: Antidepressants reduce relapse (~20%, NNT 6) in those who have achieved remission for up to 1 year when compared to placebo
- Superiority among antidepressants is controversial
- Significant placebo response rate

➢ **Role for individualizing antidepressant therapy based on patient factors?**
  ➢ Or in some cases no antidepressant therapy

INDIVIDUALIZING ANTIDEPRESSANT OPTIONS

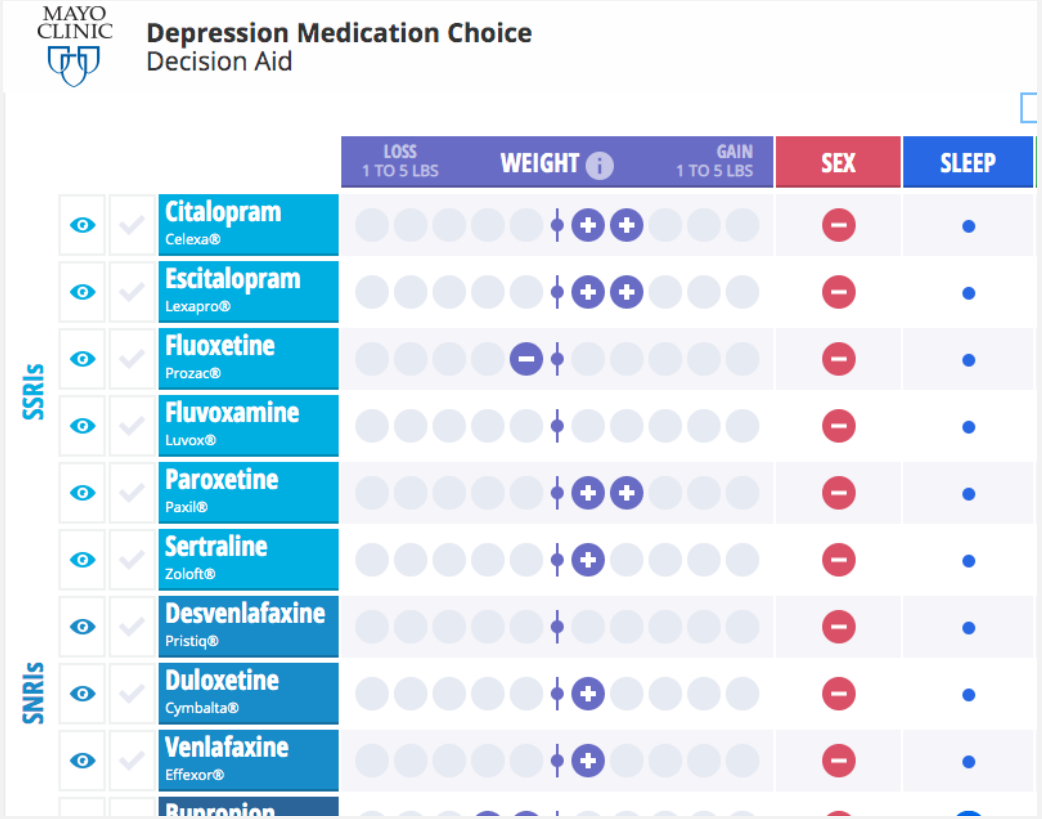
Patient Factors	Medication Factors
Clinical features and dimensions	Comparative Efficacy
Comorbid Conditions	Comparative Tolerability
Response and side effects during previous use of antidepressants	Potential Interactions with other medications
Patient preference	Simplicity of use
	Cost and availability

Kennedy 2016

SHARED DECISION MAKING

- Depression Medication Choice (DMC) - cluster randomized trial in primary care practices
  - Adults with moderate to severe depression considering treatment with an antidepressant
  - Antidepressant Treatment DMC decision aid vs Usual Care
  - PATIENTS with DMC:
    - improved decisional comfort (DMC, 80% vs UC, 75%; P = .02)
      increased knowledge (DMC, 65% vs UC, 56%; P = .03)
      improved involvement (DMC, 47% vs UC, 33%; P<.001).
  - CLINICIANS with DMC:
    - Improved decisional comfort (DMC, 80% vs UC, 68%; P < .001)
      improved satisfaction (RR, 1.64; P = .02)

https://depressiondecisionaid.mayoclinic.org/



Leblanc 2015

PILOT ANTIDEPRESSANT DECISION-SUPPORT TOOL

Adult Depression Antidepressant Treatment based on Efficacy and Comorbidities

Tracy Chin, PharmD, ACPR

Depression Specifiers[30]

Sleep Disturbances[30]	Cognitive Dysfunction[30]	Anxious distress[30]	Somatic symptoms[30]	
			Fatigue	Pain
• mirtazapine	• Vortioxetine • SSRIs (vs Placebo) • Duloxetine • Bupropion	• Paroxetine • Duloxetine • Sertraline • Escitalopram • Venlafaxine	• Duloxetine • Bupropion • SSRIs (vs Placebo)	• duloxetine • Venlafaxine • desvenlafaxine

No Depression specifiers

No Comorbidities

ANY first line agent[30]

- SSRI: citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline
- SNRI: desvenlafaxine, duloxetine, venlafaxine
- Other: Bupropion, mirtazapine, vortioxetine

→ Choice based on adverse effects, cost, drug interactions and other considerations

Comorbidities present

Central Nervous System

Smoking Cessation
- **Bupropion** up to 300mg daily; combine with NRT (NNT=8)[41]

Alcohol use disorder[8]
- **Abstinence: sertraline** up to 200mg daily + Naltrexone NNT=4. no change in mood[40]
- **Mood: mirtazapine** 45mg daily 50% reduction in HAM-D and HAM-A scores[55]

ADHD
- **Bupropion** up to 450mg daily SMD -0.5 in ADHD scores[52]
- **Duloxetine** up to 60mg daily improvement in ADHD scores (limited data)[9]

Pain

Chronic Low Back Pain	**Duloxetine** 60-120mg daily ≥30% ↓ pain inconsistent (ADR NNH~6-12)[16,34]
Osteoarthritis	**Venlafaxine** 150 - 225mg ↓ 30% pain in hip and knee OA in 9/18 patients[49] **Duloxetine** 60 -120mg daily ↓ knee OA pain only NNT=7 (ADR NNH=17)[13,16,34]
Diabetic Peripheral Neuropathy (PN)	**Duloxetine** 40-120mg daily ↓ pain NNT=6 (ADR NNH@60mg =20;NNH@120mg=10)[32,34] **Venlafaxine** 150-225mg daily ↓ pain NNT=5 (limited data)[18,32,44] **Desvenlafaxine** 200-400mg daily (EXCEEDS depression dose)[32]
Fibromyalgia	**Mirtazapine** to 30mg daily. Conflicting data. ↓ pain by ≥30% NNT=7-8 vs ADR NNH=9[32,53] **Duloxetine** 60 -120mg daily ↓pain NNT=8 vs ADR NNH@60mg = 18 ;NNH@120mg=9[32,34] **SSRI (citalopram, fluoxetine, paroxetine)** ↓ pain NNT=10 (95% CI 5-100)[32] **Venlafaxine** - limited benefit (no RCT)[32]
Chemotherapy -Induced PN	**Duloxetine** 60mg daily ↓ pain (-0.73 vs placebo) (NNT=5)[47]

Migraine Prophylaxis
- **Venlafaxine** up to 150mg daily small RCT equivalent to TCA[10,39]
- **Duloxetine** 60 to 120mg daily ↓ number of headache days (limited data)[56]

Cardiovascular

Heart Failure
- **Sertraline safe.** No significant mood benefit[37]

ACS
- **Escitalopram** 5 -20mg daily ↓ MACE (MI) post ACS NNT=8 over 8 years[29]
- **Sertraline Safe.** No significant CV benefits underpowered for mood outcomes[22]

Gastrointestinal

Liver disease
- **Hep C + Interferon: SSRIs** (citalopram up to 20mg daily; weak data)[31]

IBS (constipation and abdominal pain)
- **Paroxetine, fluoxetine, citalopram** NNT=5 -6 for ↓ global IBS symptoms over 12 weeks, Non-Significant for abdominal pain[30]

Genitourinary

Loss of Libido in women
- **Bupropion** 150mg daily OR=3.2 (2.1–6.3) 'meaningful improvement'(NNT 2)[45]

Stress incontinence
- **Duloxetine** QoL improvement (SMD –0.13) NNT=8 and ↓ no. of episodes (ADR NNH =7)[21,35]

Renal

Non-Dialysis CKD
- **Sertraline** to 200mg daily. no mood benefit. ↑ GI symptoms (NNH=8-9)[24]

Dialysis CKD
- **Sertraline** to 200mg daily. ↓ QIDS-C at 12 weeks vs.CBT (-1.84, p=0.035)[36]

ESRD-associated Pruritis[7]
- **sertraline** (58% ↓pruritis score from severe to mild)[7]
- **mirtazapine** 15mg daily(Limited data)[7,20]

Considerations in Antidepressant Decision Making

Tracy Chin, PharmD, ACPR

Adverse Effects [12,46]

Headache[51]	•**Most likely:** bupropion, escitalopram •**Likely:** SSRIs, SNRIs, vortioxetine •**Least likely**: mirtazapine
Dysrhythmia[43] and Blood Pressure[11]	•**QTc prolongation**: citalopram, escitalopram, mirtazapine (caution if baseline QTc >450ms) •**BP/HR changes:** bupropion, SNRIs neutral: SSRI, vortioxetine, mirtazapine
Sedation	•**Most Sedating**: mirtazapine (esp. at low doses) •**Possibly sedating:** SSRI, SNRI, vortioxetine •**Activating:** bupropion
GI Disturbances[38]	•**Nausea/Vomiting:** duloxetine, vortioxetine >, SNRIs>SSRIs> mirtazapine •**Constipation**: SNRIs, paroxetine, sertraline > bupropion, vortioxetine > SSRIs •**Anorexia:** SNRIs> SSRIs, vortioxetine
Sexual Dysfunction[5,14,27,42,50]	•**Most likely**: SSRI/ SNRIs (30-70%; all aspects) •**Likely:** mirtazapine, vortioxetine •**Least likely**: bupropion (may improve SSRI-induced dysfunction; SMD 1.60 vs placebo)[4]
Seizure risk[3,48]	•**Most likely:** bupropion (1/1000; dose-related) •**Unlikely :** SNRI, SSRI, mirtazapine. vortioxetine at therapeutic doses
↑ Weight[17,54]	•**Most likely**: mirtazapine (+0.4 to +2.4 kg) citalopram (+0.1 to +7.1kg) •**Less Likely to Likely** : SSRI , SNRI, vortioxetine •**Least likely:** bupropion (-2.4kg to -0.4kg)
Withdrawal Symptoms[15,25]	•**Most likely**: paroxetine, venlafaxine, desvenlafaxine •**Likely:** SNRI and SSRI •**Least likely:** fluoxetine/ vortioxetine(?) •**Potentially None**: mirtazapine, bupropion

Drug Interactions[26,28]

CYP inhibitors

- CYP 2D6: *strong*: fluoxetine, paroxetine
  moderate: bupropion, duloxetine, sertraline (>100mg)
- CYP3A4: *moderate* fluvoxamine, fluoxetine
- CYP1A2: *strong* fluvoxamine
- CYP2C19*: strong:* fluvoxamine
  moderate: fluoxetine

CYP substrates

- 2D6: vortioxetine, venlafaxine, fluvoxamine, fluoxetine, mirtazapine, paroxetine
- 2C19: citalopram, escitalopram
- 1A2: duloxetine, fluvoxamine
- 3A4: mirtazapine

Serotonin Syndrome:

Monitor: combining antidepressants with opioids, dextromethorphan, lithium, etc

Administration[2]

- **NG/OG tubes:** duloxetine, venlafaxine beads can clog smaller enteral tubes
- **ODT available**: escitalopram, mirtazapine
- **Liquid**: fluoxetine, venlafaxine (compound – div dose BID)
- **CRUSH-able:** escitalopram, sertraline (open capsule), paroxetine IR, fluvoxamine, citalopram, fluoxetine, mirtazapine (throat numbness)
- **DO NOT CRUSH:** desvenlafaxine, bupropion ER/SR, paroxetine CR, duloxetine beads, venlafaxine beads

Cost[1]

Not covered*

*by Govt of Alberta plans

- Desvenlafaxine
- Levomilnacipran
- Vilazodone

Covered

- All SSRIs
- SNRI: duloxetine, venlafaxine
- Other: mirtazapine, bupropion, Vortioxetine

Other

- **Patient's Preference**
- **Previous Antidepressant Trials**

Pharmacokinetics

Absorption[23,33]

- Structural GI changes (gastric bypass/short gut/ostomy)
- Absorption erratic with ER medications (bupropion ER, duloxetine, desvenlafaxine, venlafaxine)
- Initiation: Avoid → chose non-ER antidepressants
- Stabilized: Monitor and change if necessary

Renal Dosing[6]:

eGFR	Max Starting dose
< 60	• Bupropion 150mg/d (max daily dose) • Desvenlafaxine 50mg Q2days (eGFR<30 max daily:50mg Q2d) • Paroxetine 10mg/day
< 30	• Escitalopram 10mg/day • Sertraline 50mg/day (eGFR<15: 25mg/day) • Duloxetine 30mg/day • Venlafaxine 112.5mg/day (max daily dose) • Mirtazapine 15mg/day (max daily dose)

Hepatic Dosing[19]:

- Many agents ↑ T1/2 in hepatic impairment. Caution in dosing and reductions may be necessary
- Avoid: duloxetine, sertraline(?) in hepatic impairment

MEET PL

- 59 year old female seen at your multidisciplinary primary care clinic
- **Chief Complaint**: new Major Depressive Disorder. – moderate severity. Wants to trial an antidepressant.
- **Medical Hx:** HTN, type 1 diabetes since she was 16 years of age and mostly poorly controlled until recently, dyslipidemia, diabetic peripheral neuropathy- bothersome
- **Social Hx:** lost her job recently and on Alberta works
- **Medications at home**: rosuvastatin 5mg daily, ramipril 5mg daily, now on insulin glargine 15 units SC daily and sliding scale lispro based on carb counting , vitamin D 1000 units daily, acetaminophen 500mg PRN
- **Labs and investigations**: all within normal limits. Most current A1c: 6.4%
- **ROS**: all within normal limits
- **Compliance:** no concerns, uses dosettes, and fills medications regularly

Picture from A Place for Mom, Inc

PL CONTINUED

- Have you tried any antidepressants before?
  - Yes but it wasn't for depression. My doctor gave me something for my nerve pain. I think it was called amtrip.. Err or something like that. I remember I didn't like the side effects. It made me too groggy.
- What side effects are you most worried about?
  - I'm worried about medications that would cause me to gain weight or affect my sugars. I've worked really hard over the years to finally get my sugars under better control.
- Are costs a concern for you?
  - Yes, I lost my job in the last year and now on Alberta Works income support

Picture from https://www.aarp.org/

WHICH ANTIDEPRESSANT WOULD YOU PRESCRIBE FOR PL?

Picture from https://www.nps.org.au/consumers/antidepressants-10-things-you-should-know

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					Fatigue	Pain
• mirtazapine	• Vortioxetine • SSRIs (vs Placebo)	• Duloxetine • Bupropion	• Paroxetine • Duloxetine • Sertraline	• Escitalopram • Venlafaxine	• Duloxetine • Bupropion • SSRIs (vs Placebo)	• duloxetine • Venlafaxine • desvenlafaxine

No Depression specifiers

No Comorbidities

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Liver disease
- **Hep C + Interferon: SSRIs** (citalopram up to 20mg daily; weak data)[31]

IBS (constipation and abdominal pain)
- **Paroxetine, fluoxetine, citalopram** NNT=5 -6 for ↓ global IBS symptoms over 12 weeks, Non-Significant for abdominal pain[30]

Genitourinary

Loss of Libido in women
- **Bupropion** 150mg daily OR=3.2 (2.1–6.3) 'meaningful improvement'(NNT 2) [45]

Stress incontinence
- **Duloxetine** QoL improvement (SMD –0.13) NNT=8 and ↓ no. of episodes (ADR NNH =7)[21,35]

Renal

Non-Dialysis CKD
- **Sertraline** to 200mg daily. no mood benefit. ↑ GI symptoms (NNH=8-9)[24]

Dialysis CKD
- **Sertraline** to 200mg daily. ↓ QIDS-C at 12 weeks vs.CBT (-1.84, p=0.035)[36]

ESRD-associated Pruritis[7]
- **sertraline** (58% ↓pruritis score from severe to mild)[7]
- **mirtazapine** 15mg daily(Limited data)[7,20]

Pain

Chronic Low Back Pain	**Duloxetine** 60-120mg daily ≥30% ↓ pain inconsistent (ADR NNH~6-12)[16,34]
Osteoarthritis	**Venlafaxine** 150 - 225mg ↓ 30% pain in hip and knee OA in 9/18 patients[49] **Duloxetine** 60 -120mg daily ↓ knee OA pain only NNT=7 (ADR NNH=17)[13,16,34]
Diabetic Peripheral Neuropathy (PN)	**Duloxetine** 40-120mg daily ↓ pain NNT=6 (ADR NNH@60mg =20;NNH@120mg=10)[32,34] **Venlafaxine** 150-225mg daily ↓ pain NNT=5 (limited data)[18,32,44] **Desvenlafaxine** 200-400mg daily (EXCEEDS depression dose)[32]
Fibromyalgia	**Mirtazapine** to 30mg daily. Conflicting data. ↓ pain by ≥30% NNT=7-8 vs ADR NNH=9[32,53] **Duloxetine** 60 -120mg daily ↓pain NNT=8 vs ADR NNH@60mg = 18 ;NNH@120mg=9[32,34] **SSRI (citalopram, fluoxetine, paroxetine)** ↓ pain NNT=10 (95% CI 5-100)[32] **Venlafaxine** - limited benefit (no RCT)[32]
Chemotherapy -Induced PN	**Duloxetine** 60mg daily ↓ pain (-0.73 vs placebo) (NNT=5)[47]

Migraine Prophylaxis
- **Venlafaxine** up to 150mg daily small RCT equivalent to TCA[10,39]
- **Duloxetine** 60 to 120mg daily ↓ number of headache days (limited data) [56]

Adult Depression Antidepressant Treatment based on Efficacy and Comorbidities

Tracy Chin, PharmD, ACPR

Considerations in Antidepressant Decision Making

Tracy Chin, PharmD, ACPR

Adverse Effects [12,46]

Headache[51]	•**Most likely:** bupropion, escitalopram •**Likely:** SSRIs, SNRIs, vortioxetine •**Least likely**: mirtazapine
Dysrhythmia[43] and Blood Pressure[11]	•**QTc prolongation**: citalopram, escitalopram, mirtazapine (caution if baseline QTc >450ms) •**BP/HR changes:** bupropion, SNRIs neutral: SSRI, vortioxetine, mirtazapine
Sedation	•**Most Sedating**: mirtazapine (esp. at low doses) •**Possibly sedating:** SSRI, SNRI, vortioxetine •**Activating:** bupropion
GI Disturbances[38]	•**Nausea/Vomiting:** duloxetine, vortioxetine >, SNRIs>SSRIs> mirtazapine •**Constipation**: SNRIs, paroxetine, sertraline > bupropion, vortioxetine > SSRIs •**Anorexia:** SNRIs> SSRIs, vortioxetine
Sexual Dysfunction[5,14,27,42,50]	•**Most likely**: SSRI/ SNRIs (30-70%; all aspects) •**Likely:** mirtazapine, vortioxetine •**Least likely**: bupropion (may improve SSRI-induced dysfunction; SMD 1.60 vs placebo)[4]
Seizure risk[3,48]	•**Most likely:** bupropion (1/1000; dose-related) •**Unlikely :** SNRI, SSRI, mirtazapine. vortioxetine at therapeutic doses
↑ Weight[17,54]	•**Most likely**: mirtazapine (+0.4 to +2.4 kg) citalopram (+0.1 to +7.1kg) •**Less Likely to Likely** : SSRI , SNRI, vortioxetine •**Least likely:** bupropion (-2.4kg to -0.4kg)
Withdrawal Symptoms[15,25]	•**Most likely**: paroxetine, venlafaxine, desvenlafaxine •**Likely:** SNRI and SSRI •**Least likely:** fluoxetine/ vortioxetine(?) •**Potentially None**: mirtazapine, bupropion

Drug Interactions[26,28]

CYP inhibitors

- CYP 2D6: *strong*: fluoxetine, paroxetine
  moderate: bupropion, duloxetine, sertraline (>100mg)
- CYP3A4: *moderate* fluvoxamine, fluoxetine
- CYP1A2: *strong* fluvoxamine
- CYP2C19*: strong:* fluvoxamine
  moderate: fluoxetine

CYP substrates

- 2D6: vortioxetine, venlafaxine, fluvoxamine, fluoxetine, mirtazapine, paroxetine
- 2C19: citalopram, escitalopram
- 1A2: duloxetine, fluvoxamine
- 3A4: mirtazapine

Serotonin Syndrome:

Monitor: combining antidepressants with opioids, dextromethorphan, lithium, etc

Administration[2]

- **NG/OG tubes:** duloxetine, venlafaxine beads can clog smaller enteral tubes
- **ODT available**: escitalopram, mirtazapine
- **Liquid**: fluoxetine, venlafaxine (compound – div dose BID)
- **CRUSH-able:** escitalopram, sertraline (open capsule), paroxetine IR, fluvoxamine, citalopram, fluoxetine, mirtazapine (throat numbness)
- **DO NOT CRUSH:** desvenlafaxine, bupropion ER/SR, paroxetine CR, duloxetine beads, venlafaxine beads

Cost[1]

Not covered*

*by Govt of Alberta plans

- Desvenlafaxine
- Levomilnacipran
- Vilazodone

Covered

- All SSRIs
- SNRI: duloxetine, venlafaxine
- Other: mirtazapine, bupropion, Vortioxetine

Other

- **Patient's Preference**
- **Previous Antidepressant Trials**

Pharmacokinetics

Absorption[23,33]

- Structural GI changes (gastric bypass/short gut/ostomy)
- Absorption erratic with ER medications (bupropion ER, duloxetine, desvenlafaxine, venlafaxine)
- Initiation: Avoid → chose non-ER antidepressants
- Stabilized: Monitor and change if necessary

Renal Dosing[6]:

eGFR	Max Starting dose
< 60	• Bupropion 150mg/d (max daily dose) • Desvenlafaxine 50mg Q2days (eGFR<30 max daily:50mg Q2d) • Paroxetine 10mg/day
< 30	• Escitalopram 10mg/day • Sertraline 50mg/day (eGFR<15: 25mg/day) • Duloxetine 30mg/day • Venlafaxine 112.5mg/day (max daily dose) • Mirtazapine 15mg/day (max daily dose)

Hepatic Dosing[19]:

- Many agents ↑ T1/2 in hepatic impairment. Caution in dosing and reductions may be necessary
- Avoid: duloxetine, sertraline(?) in hepatic impairment

WHICH ANTIDEPRESSANT WOULD YOU PRESCRIBE FOR PL?

- *Zoom poll*

A) Amitriptyline

B) Mirtazapine

C) Levomilnacipran

D) Duloxetine

E) No idea, offer her a pony

SUMMARY

- Many screening tools available and all have various types of utility
  - Pragmatic vs research
  - Validation of tools In specific comorbidities
- Superiority among antidepressants is controversial
- Role for individualized antidepressant therapy and shared decision making?
  - PETRUSHKA trial underway
  - Pilot Decision-support tool

QUESTIONS?

THANK YOU!

- Email: Tracy.t.chin@albertahealthservices.ca

Photo from: https://madisonmountaineering.com/tag/summit-bid/

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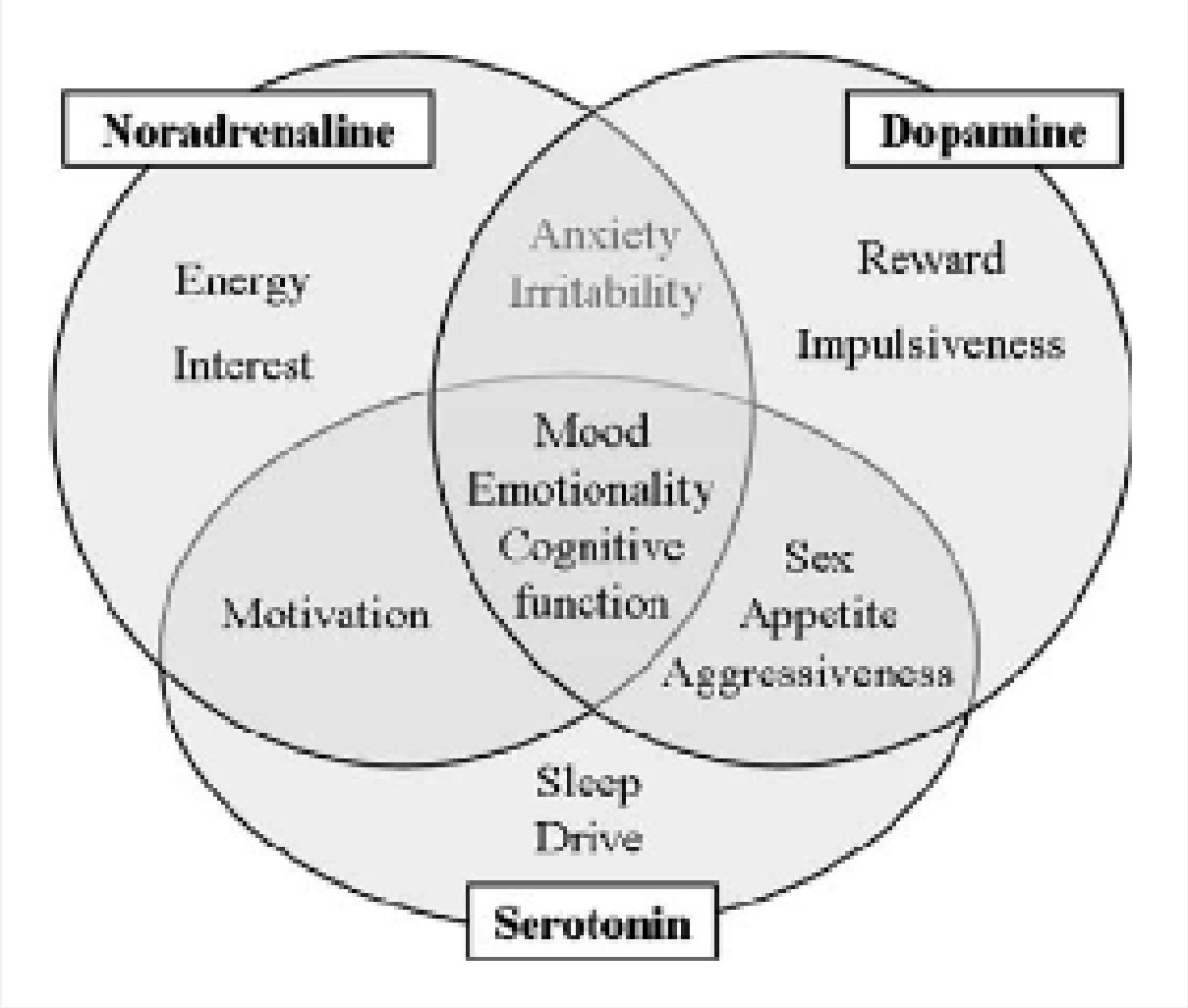
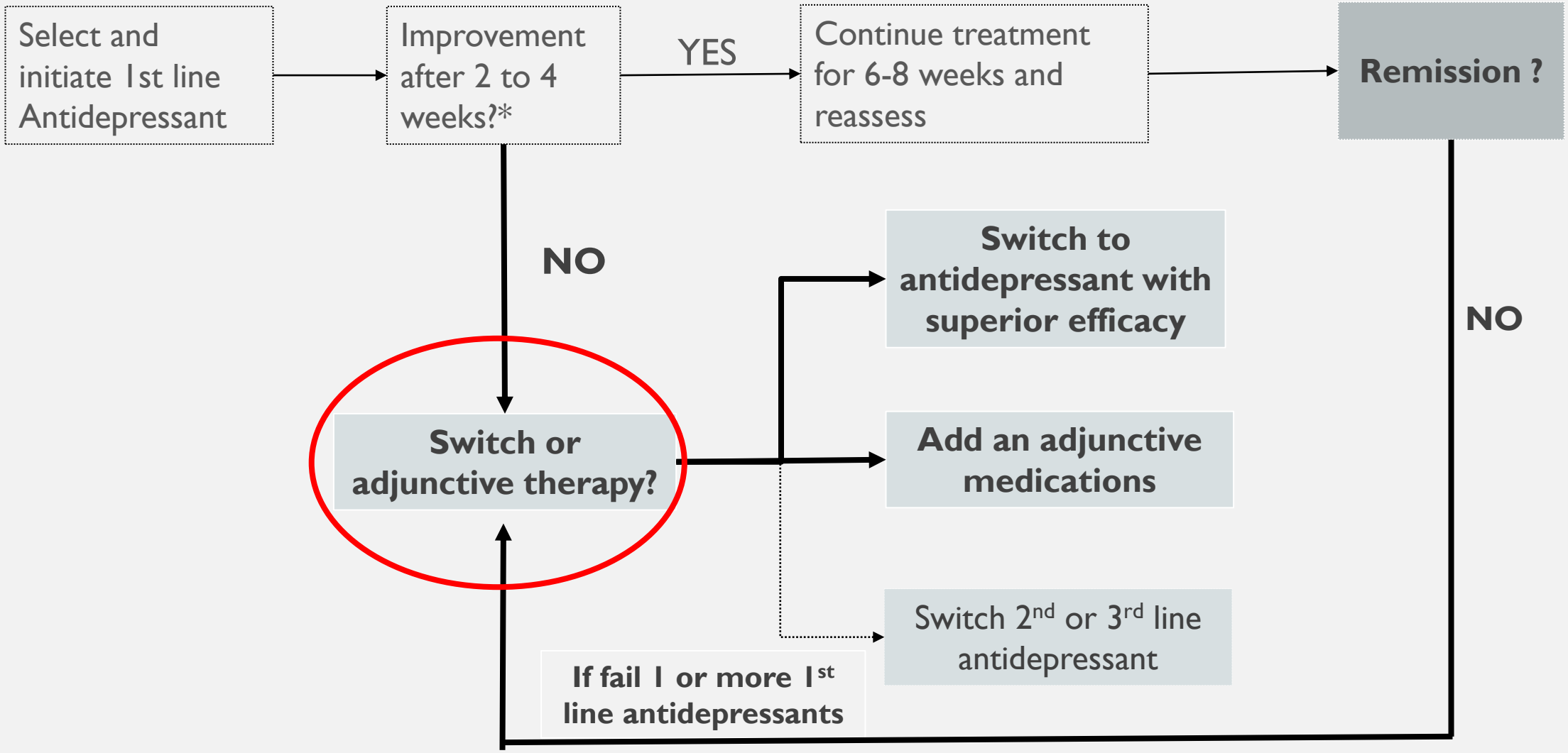
REVIEW: MONOAMINE HYPOTHESIS



Lannie 2009

WHAT IF THE AGENT YOU CHOOSE DOESN'T WORK?

PHARMACOTHERAPY TREATMENT ALGORITHM



Kennedy 2016

INADEQUATE RESPONSE: TO ADD OR TO SWITCH

Switch Antidepressants	Add Adjunctive Therapies
• First antidepressant trial	• 2 or more antidepressant trials
• Poorly tolerated side effects	• Initial antidepressant is well tolerated
• No response to antidepressant in 2-4 weeks at therapeutic dose	• Partial response (>25% improvement) to initial antidepressant
• Less severe (time to wait for response while switching)	• Specific residual symptoms or side effects that can be targeted
• Patient preference	• More severe (less time to wait for response from switching)
	• Patient preference

Kennedy 2016

STAR*D RESULTS

		Remission Rate (% difference in QIDS-SR 16 at entry and exit)	Weeks to remission
Step 1 -Citalopram only		**36.8** (vs step 2; P<0.001)	**6.3**
Step 2		**30.6** (vs step 3; P<0.001)	**5.4**
Switch:		27	5.4
-bupropion -sertraline	-venlafaxine -CBT		
Augmentation :		35.0	5.5
-bupropion -buspirone	-CBT		
Step 3		**13.7**	**5.6**
Switch		10.7	6
-nortriptyline	-mirtazapine		
Augmentation		20.5	5.3
-lithium	-liothyronine		
Step 4		**13**	**7.4**

Sackeim 2006

VAST-D

	Multisite, randomized, single-blind, parallel-assignment trial (1:1:1) 12 weeks acute phase, up to 36 weeks continuation
P	• Adult Veterans Health Administration patients with an MDD diagnosis (DSM-IV-TR) referred by clinician • suboptimal response to a treatment SSRI, SNRI, or mirtazapine (≥3 weeks stable "optimal" dose) N=1522 Mean age 54.4 years, **85.2% men**
I	Switch to bupropion SR (up to 200mg BID) (N_{switch}=511)
C	• Augment current therapy with bupropion (up to 200mg BID) N=506 • Augment current therapy with aripiprazole (up to 15mg po daily) N_{AAug} =505
O	**Primary outcome:** remission acute treatment @12 weeks (QIDS-C_{16} ≤5 at 2 visits). N_{AAug} 28.9% (n = 146) vs N_{switch} 22.3%(n = 114) RR=1.30 (1.05-1.60); *P* = .02 **NNT =15** N_{BAug} 26.9% (n = 136)vs N_{switch} and N_{BAug} vs N_{AAug} → NS differences **Secondary outcomes:** Relapse: no difference between groups Adverse effects: no significant difference in serious adverse events • Bupropion groups: more anxiety • Aripiprazole group: more somnolence, akathisia, and weight gain (9.5% significant weight gain@12wks)
Comment	Funded by Veterans affairs and aripiprazole provided by Bristol-Myers Squibb PTSD ~45-50% of patients Small to moderate effect size with augmentation of aripiprazole vs adverse effects?

Mohamed 2017

ADJUNCTIVE THERAPIES

Agent	Class	Daily Dose
First Line		
Aripiprazole	Atypical antipsychotic	2-15mg
Quetiapine	Atypical antipsychotic	150-300mg
Risperidone	Atypical antipsychotic	1-3mg
Second Line		
Brexpiprazole	Atypical antipsychotic	1-3mg
Bupropion	antidepressant	150-300mg
lithium	Mood stabilizer	600-1200mg (therapeutic levels)
Mirtazapine	Antidepressant	30-60mg
Modafinil	CNS stimulant	100-400mg
Olanzapine	Atypical antipsychotic	2.5-10mg
liothyronine	Thyroid replacement	25-50mcg
Third Line		
Stimulants, other antidepressants, Ziprasidone		
Tri-cyclic antidepressants		

Kennedy 2016

COMPARATIVE EFFICACY, ACCEPTABILITY, AND TOLERABILITY OF AUGMENTATION AGENTS IN TREATMENT-RESISTANT DEPRESSION

	Network meta-analysis of published RCTs (included 48 trials)
P	adult patients with treatment-resistant depression(n=6,654 participants)
I	aripiprazole, bupropion, buspirone, lamotrigine, lithium, methylphenidate, olanzapine, pindolol, quetiapine, risperidone, and thyroid hormone
C	Each other and placebo
O	**Primary outcome: 50% reduction or more on depression scale in study (vs. placebo)** quetiapine (OR = 1.92; 95% CI, 1.39-3.13)* aripiprazole (OR = 1.85; 95% CI, 1.27-2.27)* thyroid hormone (OR = 1.84; 95% CI, 1.06-3.56) lithium (OR = 1.56; 95% CI, 1.05-2.55) **Tolerability (vs. placebo):** quetiapine (OR = 3.85; 95% CI, 1.92-8.33) olanzapine (OR = 3.36; 95% CI, 1.60-8.61) aripiprazole (OR = 2.51; 95% CI, 1.11-7.69) lithium (OR = 2.30; 95% CI, 1.04-6.03)
Comments	Quality of studies overall moderate to poor. Limited head to head comparisons

Significantly less well tolerated than placebo

* Quetiapine and aripiprazole more robust than thyroid hormone and lithium

Zhou 2015

MIRTAZAPINE STUDIES

- RCT (*n* = 60), mirtazapine combined with paroxetine showed good tolerance and significantly better response compared with high doses of either agent alone (Debonnel 2000)
- An open-label study (*n* = 20) followed by a small RCT (*n* = 26) of mirtazapine 15–30 mg in combination with other antidepressants (including SSRIs) at near-maximum doses revealed a significant response and good tolerance (Carpenter,2002).
- Pragmatic study mirtazapine vs placebo = No difference (Kessler, 2018)

Debonnel, G, Gobbi, G, Turcotte, J et al (2000) Effects of mirtazapine, paroxetine and their combination: a double-blind study in major depression. *European Neuropsychopharmacology*; 10: 252

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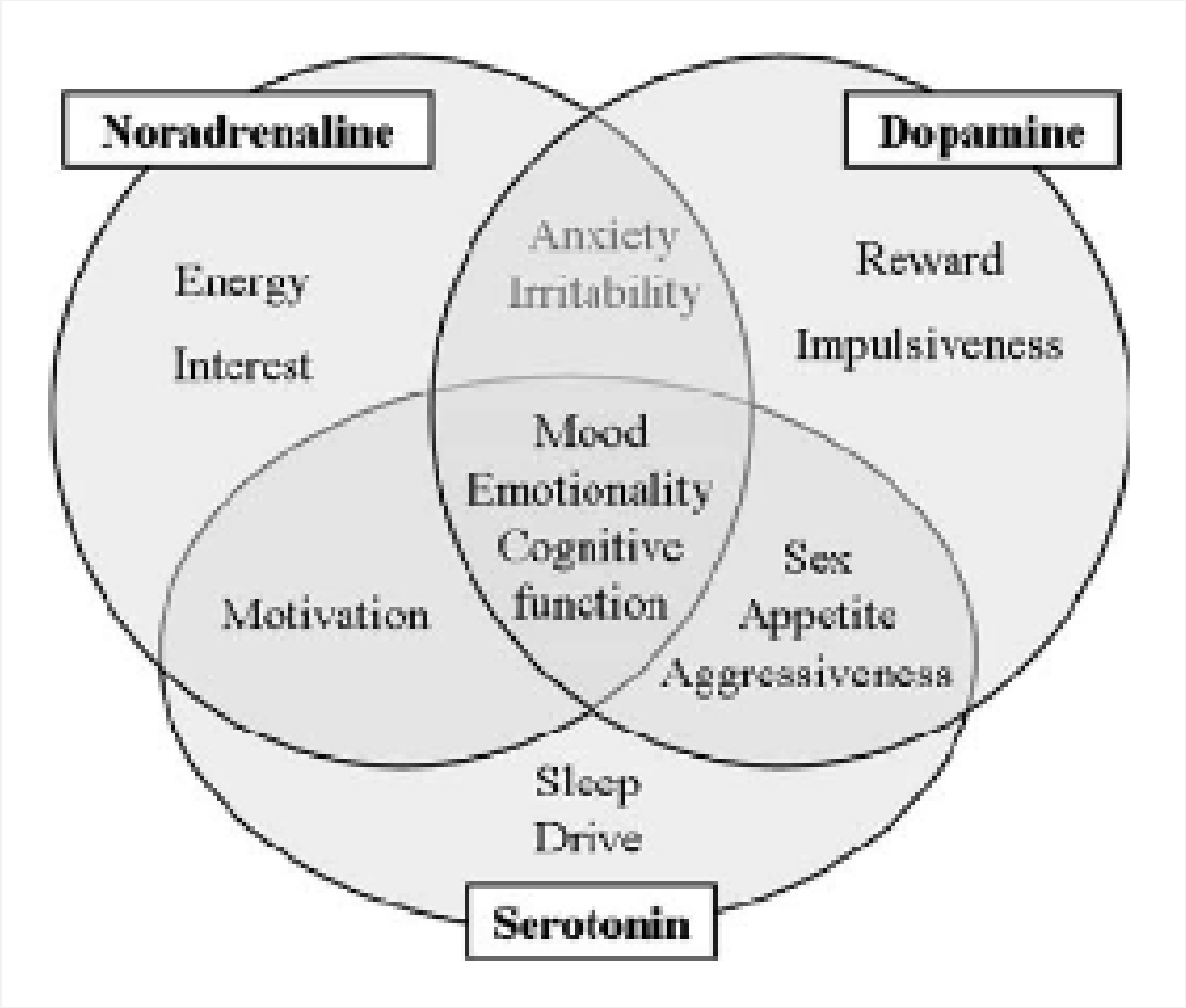
Mirtazapine added to SSRIs or SNRIs for treatment resistant depression in primary care: phase III randomised placebo controlled trial (MIR) *Kessler et al BMJ* 2018; 363 doi: https://doi.org/10.1136/bmj.k4218

WHATS NEXT?

- Piloting tool in practice to assess utility and impact in antidepressant decision-making
- Making tool electronic → app?
- Expanding information
  - Include: special populations, adjunctive medications, switching antidepressants, second-line therapies
- Study on patient satisfaction and engagement in depressant treatment before and after tool
- Development of Patient education tools ie) infographics on treatment expectations

REVIEW: MONOAMINE HYPOTHESIS



Lannie 2009

LEVOMILNACIPRAN

Mechanism of Action:

- S**N**RI

Indication:

- Major Depressive Disorder (2nd line-CANMAT)

Common Adverse Reactions:

- nausea/vomiting, constipation, hyperhidrosis, tachycardia/ palpitations, HR increased, erectile dysfunction/ ejaculation disorder

Features that set it apart:

- more norepinephrine reuptake inhibitor vs other SNRIs, low potential for drug interactions

Lexicomp 2021
McIntyre 2017

VORTIOXETINE

Mechanism of action:

- Multi-modal (SRI; $5HT_{1A}$ agonist; $5HT_{1B}$ partial agonist; $5HT_{1D}$, $5HT_3$, and $5HT_7$ antagonist)

Indication:

- Major Depressive Disorder (1st line-CANMAT)

Common Adverse reactions:

- Nausea, diarrhea, dry mouth, dizziness, constipation, vomiting

Features that set it apart:

- less sexual side effects, improve cognitive function?, first line in CANMAT, studied in elderly

McIntyre 2014
McIntyre 2017

UPDATED THEORIES OF DEPRESSION

- Neurotrophic Hypothesis
  - Depression is a result from disruption in synaptic plasticity
  - Antidepressants, electroconvulsive therapy may improve synaptic plasticity
- Abnormalities in glutamatergic signaling
  - Ketamine, an NMDA receptor antagonist, demonstrated effectiveness in treating antidepressant-resistant patients rapidly and reduced suicidal ideation

Lanni 2009

ESKETAMINE

Mechanism of action:

- NMDA receptor antagonist and AMPA receptor agonist

Dosing :

- Induction: intranasally twice weekly for 4 weeks. Maintenance: Intranasally once weekly or once every 2 weeks
- Mandatory: administered with direct medical supervision and 2 hr monitoring

Kinetics:

- Half-life elimination: 7 to 12 hours (Time to peak:20 to 40 minutes)

Common Adverse Effects (1-4 hours post dose):

- nausea/vomiting, dizziness, sedation, **dissociation**, headache, **increase in BP**, hypoesthesia.

Cost

- **$$$$$**

Features that set it apart

- treatment resistant depression + antidepressant, intranasal administration, less frequent administration, ? decreasing suicidality,? Long term cognitive changes

Lexicomp
Spravato product monograph