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Psychiatry and Addictions Case Conference
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07/18/2019

WELCOME BACK!

Today's Topic:

Treatment Resistant Depression:

Should I augment or switch medications?

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PANELISTS:

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TREATMENT RESISTANT DEPRESSION

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GENERAL DISCLOSURES

The University of Washington School of Medicine also gratefully acknowledges receipt of educational grant support for this activity from the Washington State Legislature through the Safety-Net Hospital Assessment, working to expand access to psychiatric services throughout Washington State.

GENERAL DISCLOSURES

UW PACC is also supported by Coordinated Care of Washington

SPEAKER DISCLOSURES

- ✓ Any conflicts of interest?

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SPEAKER DISCLOSURES

✓ No conflicts of interest

PLANNER DISCLOSURES

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DEPRESSION

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OBJECTIVES

1. Review first line treatment of depression
2. Understand the basics of treatment selection
3. Discuss duration of treatment
4. Serotonin syndrome
5. Learn when to consider switching versus augmentation in treatment resistant depression
6. Review augmentation options

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TREATMENT SELECTION

- Mild depression:
  - Psychotherapy alone OR
  - Meds alone OR
  - Combination
- Moderate-Severe depression:
  - Meds alone OR
  - Meds with psychotherapy
- Psychotic depression
  - Antidepressant + Antipsychotics
  - ECT

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FIRST LINE ANTIDEPRESSANTS

SSRI

- Except Fluvoxamine

SNRI

- Except Milnacipran (Fibromyalgia)

Bupropion

Mirtazapine

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ALL ANTIDEPRESSANTS HAVE FAIRLY SIMILAR EFFICACY…

So what factors go into choosing the right antidepressant?

- patient tolerance
- Age, sex, cost
- dosing schedules (once daily, twice daily, three times daily?)
- possible drug interactions, side effects
- past response to med
- family member's response to med
- Comorbidities (medical/psychiatric)

What You Should Know

Will this medicine work for me?

- The antidepressants presented in this decision aid all work the same for treating depression.
- Most people with depression can find one that can make them feel better.
- 6 out of 10 people will feel better with the first antidepressant they try and the rest will have to try other antidepressants before they find the one that is right for them.

How long before I feel better?

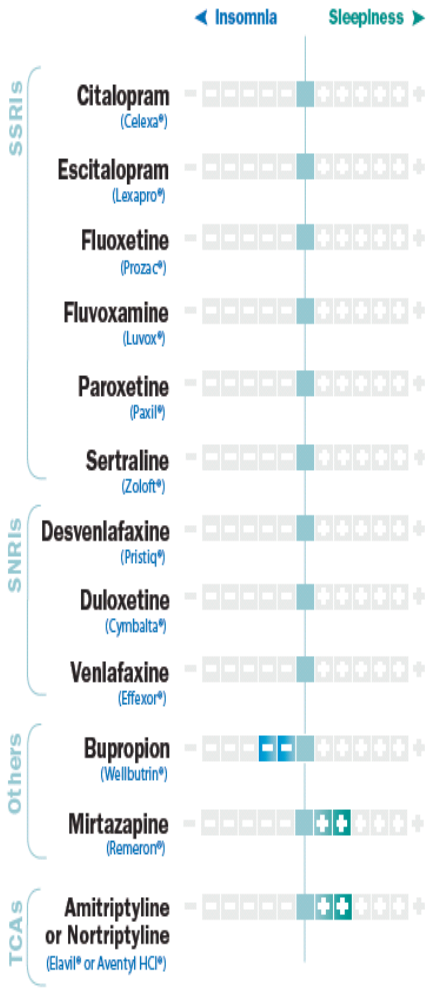
- Most people need to take an antidepressant regularly for at least 6 weeks to begin to get the full effect.

Understanding side effects

- Most people taking antidepressants have at least one side effect.
- Many side effects go away after a few weeks, but some only go away after you stop the medicine.

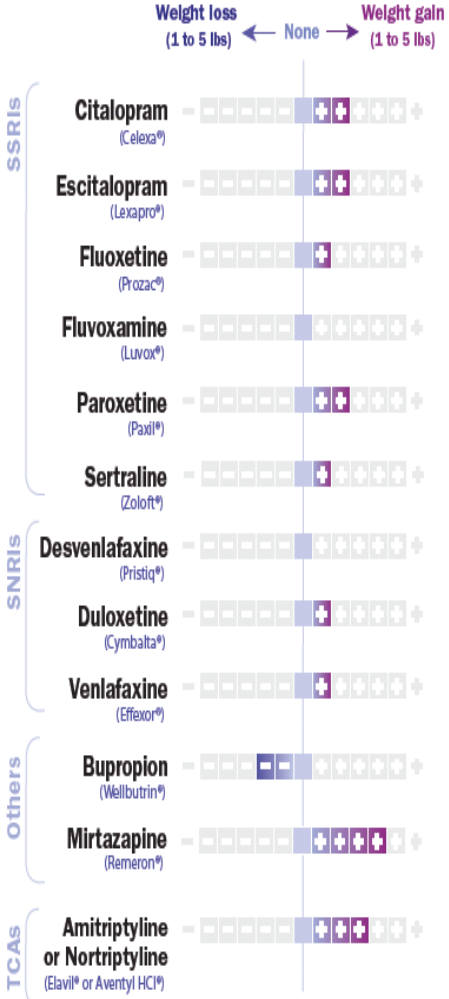
Sleep

Some people may experience sleepiness or insomnia because of their antidepressant.



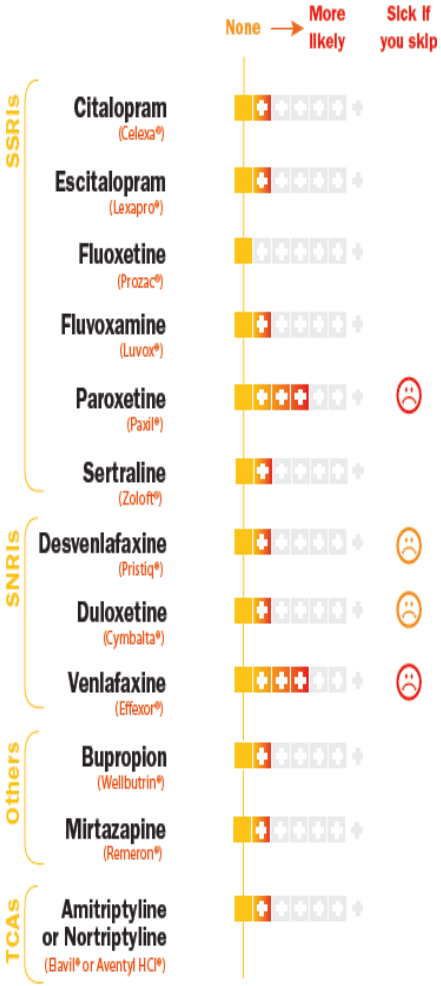
Weight Change

Some people may experience weight change. It is most likely to occur over six to twelve months and depends on your actual weight. The chart below is based on a 150 lb person.



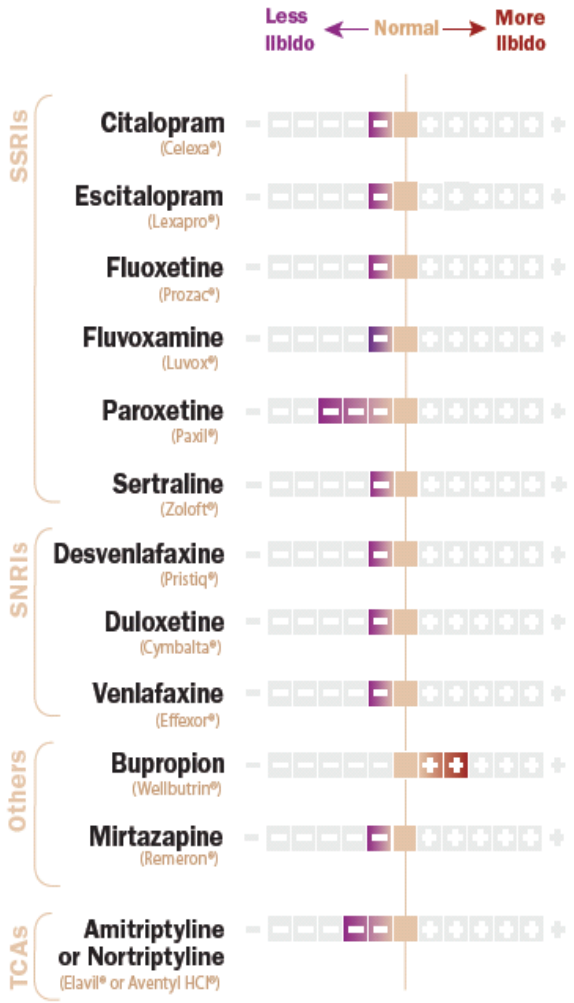
Stopping Approach

Quitting your medicine all at once can make you feel sick, as if you had the flu (e.g. headache, dizziness, light-headedness, nausea or anxiety).



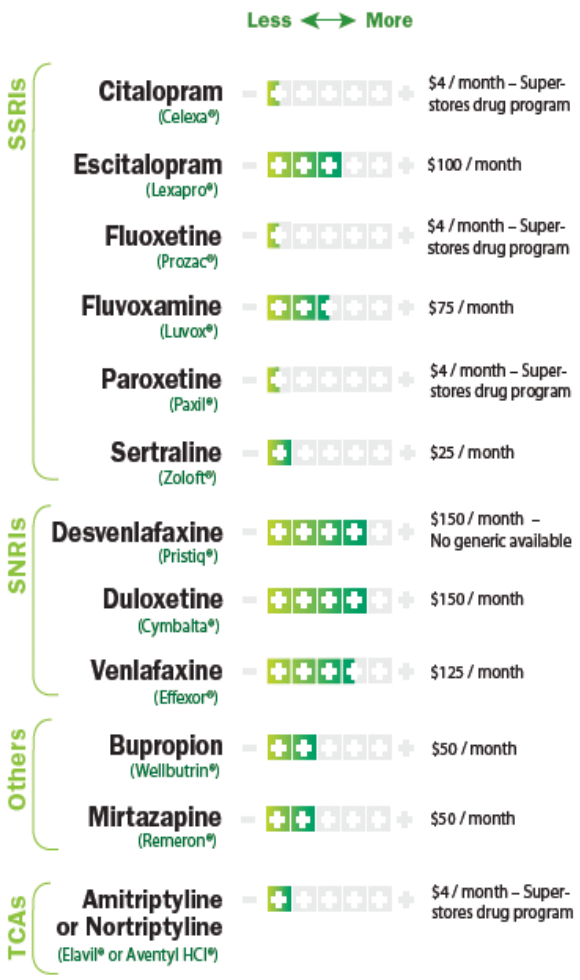
Sexual Issues

Some people may experience loss of sexual desire (libido) or loss of ability to reach orgasm because of their antidepressant.



Cost

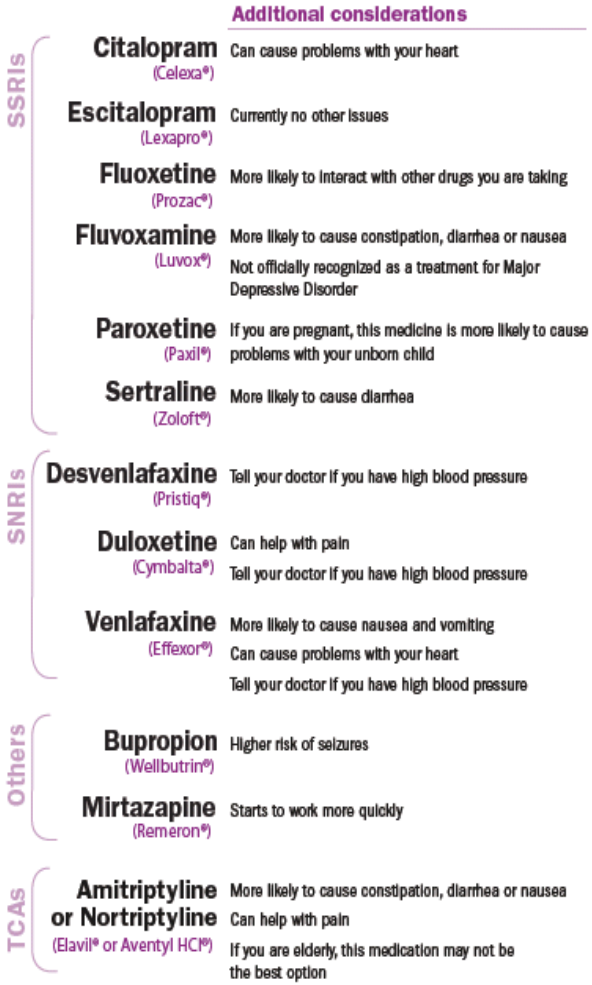
These figures are estimates and are for comparative reference only. Actual out-of-pocket costs vary over time, by pharmacy, insurance plan coverage, preparation and dosage.



Keep in Mind

Depression medicines may cause some:

- constipation, diarrhea and nausea
- increased risk of suicidal thoughts and behaviors (18- to 24-year-olds)
- harm to an unborn child
- risk of developing serotonin syndrome, a potentially life-threatening condition
- possible drug-drug interactions



ADEQUATE TRIAL

4-8 weeks on therapeutic dose

- If partial improvement in 6-12 weeks then increase the dose
- Continue for 6-12 months
- Long term use for second or third episode of depression

TREATMENT RESISTANT DEPRESSION

Unsatisfactorily response to at least 2 trials (> 6 weeks) of antidepressant monotherapy

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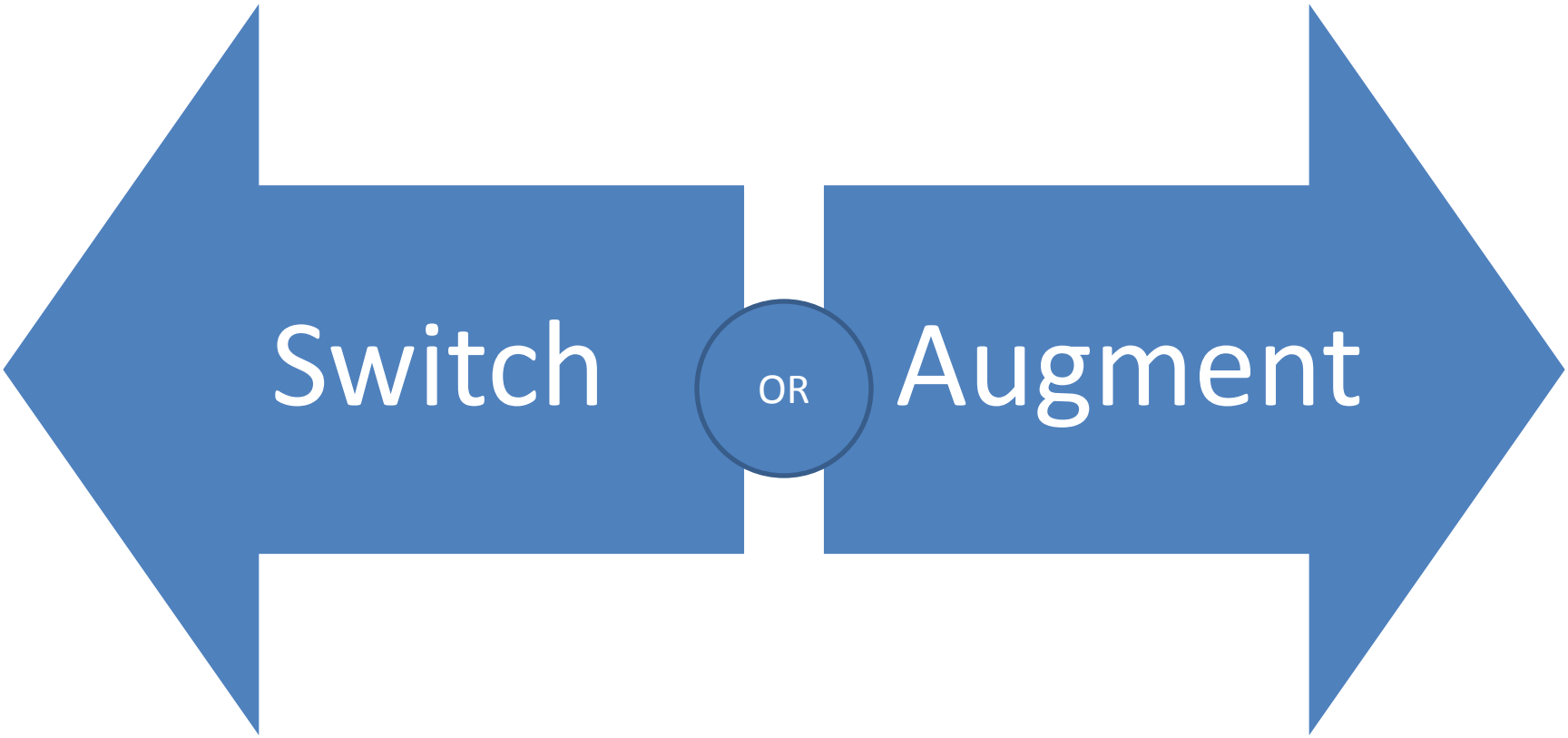
THINGS TO CONSIDER

Diagnosis

Comorbidity

Adherence

NEXT STEP



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Switch	Augment
Intolerance of adverse effects No improvement in symptoms	**Partial benefit** Adverse effects but improved symptoms

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J Clin Psychiatry. 2018 Jan/Feb;79(1). pii: 16r10749. doi: 10.4088/JCP.16r10749.

Switching the Antidepressant After Nonresponse in Adults With Major Depression: A Systematic Literature Search and Meta-Analysis.

Bschor T[1,2,3], Kern H[4], Henssler J[5], Baethge C[6].

Results: Four randomized controlled trials were included in the strict analysis and 8 in the broad analysis. In both analyses, switching was not superior to continuation: the standardized mean difference in the strict analysis was −0.17 (95% CI, −0.59 to 0.26; $P = .45$; $I^2 = 77.8\%$) and in the broad analysis was 0.031 (95% CI, −0.26 to 0.32; $P = .836$; $I^2 = 85.3\%$). All secondary outcome analyses (response and remission rates, low risk of bias studies only, leave-one-out analysis, dropouts) supported the results. There was no indication of publication bias.

REVIEW ARTICLE

See commentaries by Nierenberg et al, Kocsis, and Shelton

Comparative Efficacy, Acceptability, and Tolerability of Augmentation Agents in Treatment-Resistant Depression: Systematic Review and Network Meta-Analysis

Xinyu Zhou, PhD; Arun V. Ravindran, PhD; Bin Qin, MD; Cinzia Del Giovane, PhD; Qi Li, PhD; Michael Bauer, PhD; Yiyun Liu, MD; Yiru Fang, PhD; Tricia da Silva, MA; Yuqing Zhang, MD; Liang Fang, PhD; Xiao Wang, MD; and Peng Xie, MD

Results: A total of 48 trials consisting of 6,654 participants were eligible. In terms of the primary efficacy, quetiapine (OR = 1.92; 95% CrI, 1.39–3.13), aripiprazole (OR = 1.85; 95% CrI, 1.27–2.27), thyroid hormone (OR = 1.84; 95% CrI, 1.06–3.56), and lithium (OR = 1.56; 95% CrI, 1.05–2.55) were significantly more effective than placebo. Sensitivity analyses indicated that efficacy estimates for aripiprazole and quetiapine were more robust than those for thyroid hormone and lithium. In terms of acceptability, no significant difference was found between active agents and placebo. In terms of tolerability, compared to placebo, quetiapine (OR = 3.85; 95% CrI, 1.92–8.33), olanzapine (OR = 3.36; 95% CrI, 1.60–8.61), aripiprazole (OR = 2.51; 95% CrI, 1.11–7.69), and lithium (OR = 2.30; 95% CrI, 1.04–6.03) were significantly less well tolerated.

SWITCHING OPTIONS

- Different SSRI
- SNRI
- Mirtazapine
- Bupropion

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AUGMENTATION: OPTIONS

Bupropion or Mirtazapine

Atypical Antipsychotics

Lithium

Thyroid Hormone (T3)

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SEROTONIN SYNDROME

- It can occur after starting or increasing a single serotonergic medication or adding another med
- Other non psychiatric meds which increase serotonin:

➢ antiemetic (ondansetron, metoclopramide)

➢ antimigraine (sumatriptans)

➢ antibiotics (linezolid, ritonavir)

➢ OTC (dextromethorphan)

SEROTONIN SYNDROME

- **Mental status changes**

  confusion → agitation → delirium

- **Neuromuscular changes**

  hyperreflexia, clonus, myoclonus, shivering, tremor

- **Autonomic instability**

  tachycardia, diaphoresis, fever, diarrhea

ATYPICAL ANTIPSYCHOTIC

Strong evidence for efficacy

Aripiprazole, (brexpiprazole), **Olanzapine (in combination with fluoxetine**), **Quetiapine**, Risperidone

16 randomized trials, Remission occurred in more patients who received an adjunctive antipsychotic compared with placebo (31 versus 17 percent)

Duration: Consider taper (after response) 3-6 months to reduce exposure to side effects

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ARIPIPRAZOLE	QUETIAPINE	RISPERIDONE	OLANZAPINE (WITH FLUOXETINE)
More positive trials than other atypicals Improved functioning and quality of life *	High efficacy	Better tolerability	Olanzapine FDA approved only aug to fluoxetine.
2mg- 15mg,	start 25-50mg, max dose 300mg	start 0.25mg, max dose 3mg	in combination with fluoxetine, 6-18 mg
Akathisia	Sedation Dry Mouth Dizziness	Prolactinemia EPS Dry Mouth	Metabolic Syndrome

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Side effects	Monitoring
1. **Metabolic Syndrome**	weight, waist circumference, blood pressure, fasting plasma glucose, fasting lipid profile
2. **EPS**	AIMS
3. **Cardiovascular Events** (QTc prolongation)	EKG (Baseline, steady state, if any symptoms)
4. **Agranulocytosis**	CBC
5. **Increase risk of Mortality**	Black Box warning, 1.6-1.7 fold increase in Dementia –related psychosis

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LITHIUM AUGMENTATION

Second best augmentation except in patient at risk of suicide

Limitations: Risk of toxicity, monitoring, adverse effects

Dosing: 150-300 mg ,level 0.5-0.8

Duration: 1 year if responds

Monitoring: Li level, Cr, TSH, ECG, Ca, CBC– every 6-12 months

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LITHIUM

Interactions:

Increase Li: NSAIDS, ACE inhibitors, HCTZ, fluid loss, low Na diet .
Decrease Li: caffeine

Rapid discontinuation increases the risk of relapse and possibly suicide

Contraindications: renal impairment, hyponatremia, dehydration, significant CV disease

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THE THYROID (T3 LIOTHYRONINE)

Evidence is overall supportive but a little mixed

Predictors of response: subclinical hypothyroidism

Dosing-T3 Start at 25mcg qday. (12.5mcg in elderly) Titrate to 50mcg if needed after 1-2 weeks.

Response: within days, full-in 4-6 weeks . Duration: 1 year if working No taper needed

Monitoring: baseline TSH, 1mo and Q6 Reduce dose if TSH < lower limit of normal (0.5 mIU/L

THYROID (LIOTHYRONINE)

Side Effects: tremor, palpitations, heat intolerance, sweating, inc bowel movements, arrhythmias

Contraindications: adrenal insufficiency, unstable angina, recent MI, caution in elderly and DM (increase in insulin requirements?)

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NEWER ANTIDEPRESSANTS

Med	Target Dose	Pros	Cons
Vilazodone (Viibryd)	20-40 mg with food	Less risk of sexual side effects Less risk of weight gain	GI side effects
Vortioxetine (Trintellix)	5-20 mg	Pro-cognitive effects Less risk of weight gain	GI side effects Sexual side effects

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ELECTROCONVULSIVE THERAPY (ECT)

- Superior efficacy when compared to medication in multiple trials
- Limitations:
  - Significant side effects
  - Access
  - Stigma

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THANK YOU!

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