UNIVERSITY of WASHINGTON
PSYCHIATRY & BEHAVIORAL SCIENCES
School of Medicine

"TREATMENT-RESISTANT" DEPRESSION: WHAT TO DO WHEN DEPRESSION TREATMENT ISN'T WORKING

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OVERVIEW OF SESSION

- Why do depression treatments not work?
- Cases to illustrate evidence-based strategies to adjust or intensify treatment

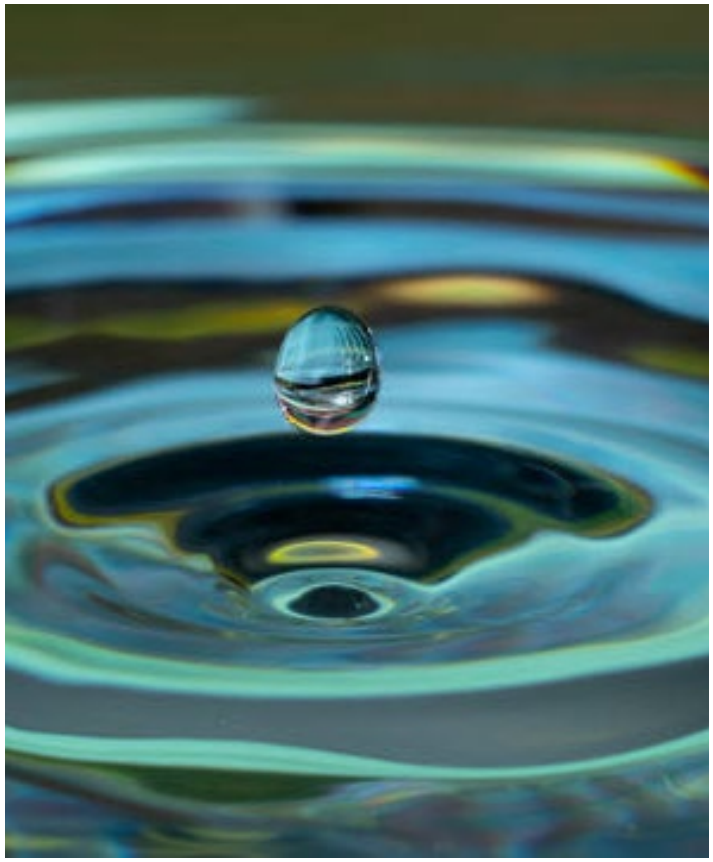
OBJECTIVES

By the end of this session, participants will

1. Understand the prevalence and impact of treatment-resistant depression;
2. Learn at least two evidence-based strategies to intensify depression treatment;
3. Consider role of somatic therapies in their treatment of depression

IMPACT OF DEPRESSION

- Depression is leading cause of disability globally
- Economic costs of depression in US in 2018: $236 Billion
- 14% of US population (4.9 million adults) in received antidepressant prescription in past 30 days



Brody D and Gu Q. NCHS Data Brief No. 377, September 2020; US CDC
Greenberg, P.E., et al. Pharmacoeconomics. 2021 May 5;1-13

TREATMENT-RESISTANT DEPRESSION

- Not a discrete biological entity
- No universally-accepted definition
- Commonly operationalized as depression that fails to respond to 2 or more adequate trials of antidepressant meds (mechanistically dissimilar)

Gaynes BN et al. Defining treatment-resistant depression. Depress Anxiety. 2020 Feb;37(2): 134-145.
Dodd S et al. The World Journal of Biological Psychiatry,2021: 22:7, 483-494

WHY DO TREATMENTS FAIL?

- Pharmacokinetic factors
- Non-Adherence
- Wrong diagnosis
  - Substance-induced use: alcohol, cannabis
  - Medical: OSA, TSH
  - Psychiatric: Bipolar disorder?
- Co-morbidity: anxiety (PTSD), personality disorder

ADHERENCE

Improving our Patient's Health Outcomes

It's not just ***IF*** a patient is non-adherent, but ***WHY***

- 15% of people prescribed an SSRI never fill the prescription
- Adherence to antidepressants over time:
  - 95.5% at one month
  - 52.6% at 2 months
  - 18.9% at 3 months

Aznar-Lou I et al, J Affect Disord 2018 Jan 15 226: 282-286.
Ereshefsky L et al. J Med Econ 2010; 13(3): 527-36.

CHECKPOINT

Think about the last prescription you wrote to refill an antidepressant medication…

- How did you assess adherence?
- What were the barriers to taking medications as prescribed?

MEDICATION SIDE EFFECT CHECKLIST

Problem	Are you experiencing this?	Questions for prescriber
Nausea/ diarrhea	Y N	
Headache	Y N	
Sedation/ drowsiness/ sleeping too much	Y N	
Appetite or weight change	Y N	
Feeling jittery or restless, or needing to move around or pace	Y N	
Blurry vision, dry mouth, constipation, urinary retention	Y N	
Changes in sexual function	Y N	
Not feeling like myself	Y N	

I think the pros of using medications outweigh the cons Y N

CASE EXAMPLE

33 year-old man with depression, anxiety, migraines, and type 2 diabetes

- Chief complaint: depression. “I initially thought this medication was working great, but now I’m not so sure.”
- Current meds: sertraline 100mg daily, metformin 1000 mg twice daily
- Prior med trials: escitalopram (Lexapro) and paroxetine (Paxil)
- PHQ-9: 11 (initial 21); GAD-7: 17 (initial 18)

BEST OPTION FOR CHANGING TREATMENT?

A. Augment with venlafaxine (Effexor) 37.5mg ER daily
B. Increase sertraline to 150mg daily
C. Augment with bupropion (Wellbutrin) 150mg XL daily
D. Retrial paroxetine (Paxil) at a higher dose
E. Refer to psychotherapy

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LEARNING POINTS

- Maximize the dose (75%-100% of max dose) before considering next steps, if side effects are tolerable
- Untreated anxiety can fuel depression
  - –Anxiety symptoms may require higher doses of antidepressants
- Bupropion (Wellbutrin) can worsen anxiety
- Avoid routinely combining SSRIs and SNRIs due to risk of serotonin syndrome

SHARED DECISION MAKING

Use validated clinical rating scales to inform decision making

https://www.ahrq.gov/health-literacy/professional-training/shared-decision/tools/factsheet.html

PSYCHOTHERAPY FOR DEPRESSION

- Cognitive behavioral therapy (CBT)
  - –Behavioral activation
  - –Cognitive restructuring
- Interpersonal Psychotherapy (IPT)
- Problem-solving therapy
- Psychodynamic psychotherapy

Lopez-Lopez JA et al. Psychol Med 2019; 49 (12): 1937-1947
Zhang A, et al. J Am Board Fam Med 2018 Jan-Feb; 31(1): 139-150.
Bernecker SL et al. Clin Psychol Rev 2017 Aug; 56: 82-93.

LIGHT THERAPY

- 2500-10,000 lux for 30-60 minutes at same time every day (before 8 AM)
- Increasing exposure to natural light and increasing exercise also effective
- Inconclusive results for Vitamin D treatment

Galima et al. Am Fam Physician 2020; 102(11): 668-672

WHAT IF MAXIMUM DOSE IS NOT ENOUGH?

- Patient's anxiety and mood are further improved with sertraline 200mg but depression not completely resolved. He continues to complain of low mood and low energy as well as sexual side effects from sertraline.

- PHQ-9: 10, GAD-7: 8

WHAT IF MAXIMUM DOSE IS NOT ENOUGH?

- **What would you do next?**

A. Switch to escitalopram (Lexapro)
B. Switch to venlafaxine (Effexor)
C. Switch to bupropion (Wellbutrin)
D. Augment with buspirone (Buspar)
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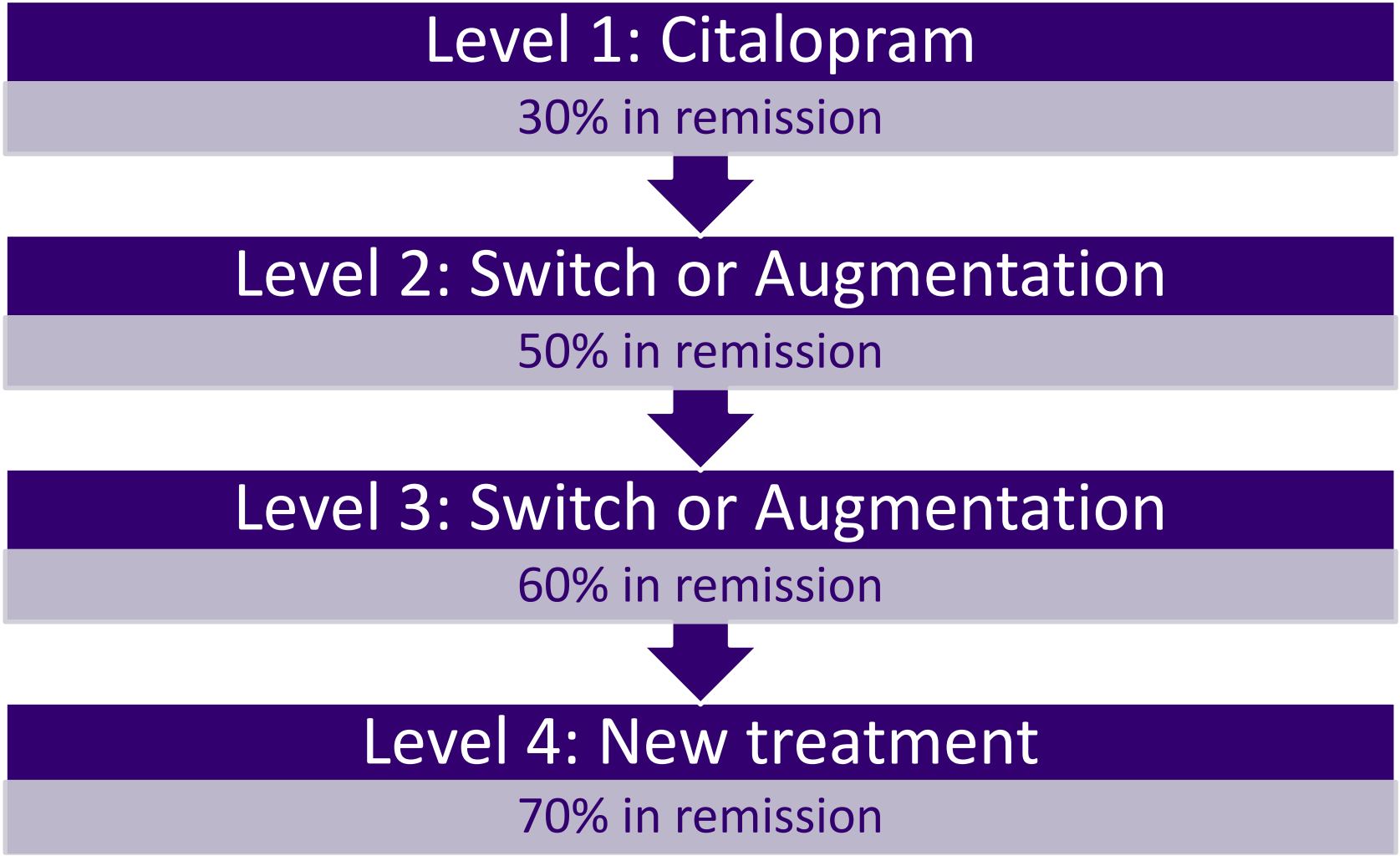
STAR*D TRIAL (2001-2006), N=4,041

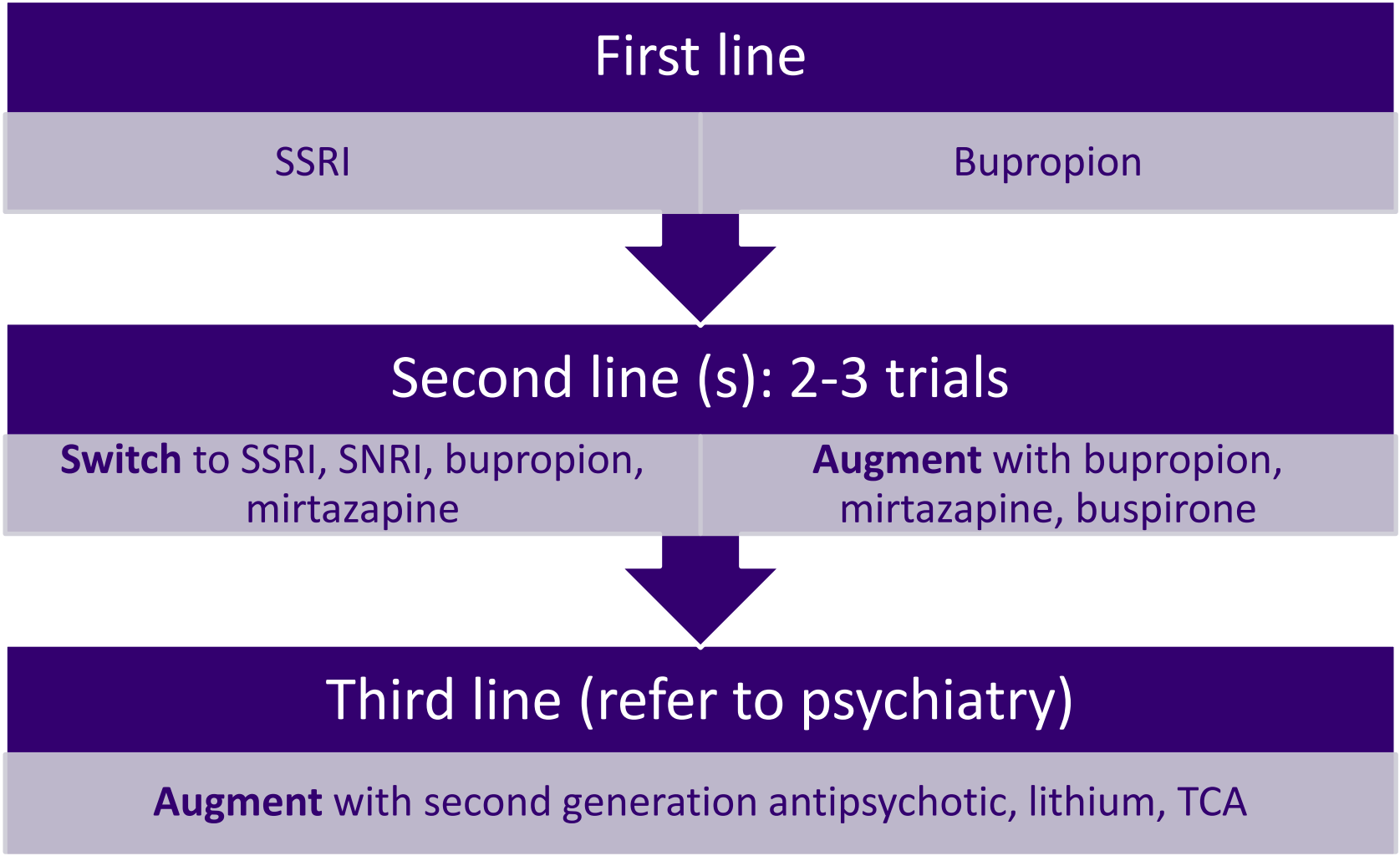


Rush AJ. Am J Psychiatry 2007 Feb;164(2):201-4

AUGMENTATION VS SWITCHING MEDS

- Neither clearly superior
- Assess remaining symptoms to target
- Consider augmenting in urgent situations (cross tapering takes weeks)
- Consider switching if patient has been on an antidepressant for years

ANTIDEPRESSANT ALGORITHM



WHICH MEDICATION?

Med	Target Symptoms	Side effects
SSRI	Sertraline: perinatal, CVD, ESRD, PTSD Fluoxetine: activating, irregular adherence Paroxetine: anticholinergic	Sertraline: diarrhea Escitalopram: minimal SEs and drug interactions Fluoxetine: 2D6 interactions
Bupropion	Activating, helps concentration, reduce sexual SEs, smoking cessation	Anxiety, insomnia, lowers seizure threshold (avoid if h/o seizure, eating disorder)
SNRI	Venlafaxine: pain Duloxetine: pain, fibromyalgia, migraines	HTN, withdrawal
Mirtazapine	Insomnia, low appetite/nausea, less likely sexual SEs	Weight gain
Buspirone	Anxiety, helps reduce sexual SEs	Minimal
Tricyclic	Nortriptyline, amitriptyline: pain, migraines, insomnia, anxiety	Sedation, anticholinergic SEs

PRINCIPLES OF SAFE PRESCRIBING

Choosing Wisely

An initiative of the ABIM Foundation

1	Don’t routinely prescribe antipsychotic medications as a first-line intervention for insomnia in adults.
2	Don’t routinely use antipsychotics as first choice to treat behavioral symptoms of dementia.
3	Don’t routinely prescribe to treat behavioral symptoms of childhood mental disorders in the absence of approved or evidence supported indications
4	Don’t routinely prescribe two or more antipsychotic medications concurrently
5	Don’t prescribe antipsychotic medications for any indication without initial evaluation and ongoing monitoring.

https://www.choosingwisely.org

CHECKPOINT

Think about your own practice…

How long do you treat an episode of depression?

- Systematic monitoring
- Criteria for stopping medication

DURATION OF TREATMENT

- Monitor every 1-3 months with PHQ9
- Continue 9 months after remission if no prior episodes or risk factors
- Consider longer term maintenance if:
  - Two or more previous episodes
  - Prior episodes were severe (hospitalization, suicidality)
  - Presence of residual symptoms
  - Ongoing psychosocial stressors
  - Early age at onset
  - Family history of mood disorders

APA Guidelines 2010; Dartmouth Guidelines 2017

SAFETY ASSESSMENT TEMPLATE

Predisposing risk factors:

Dynamic risk factors:

Protective risk factors:

Imminence:

Overall risk:

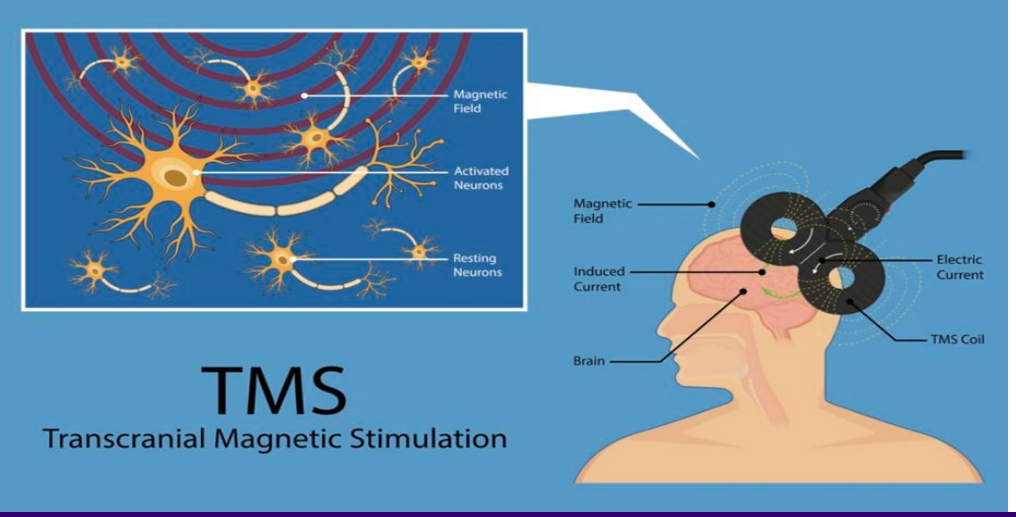
Justification for level of care:

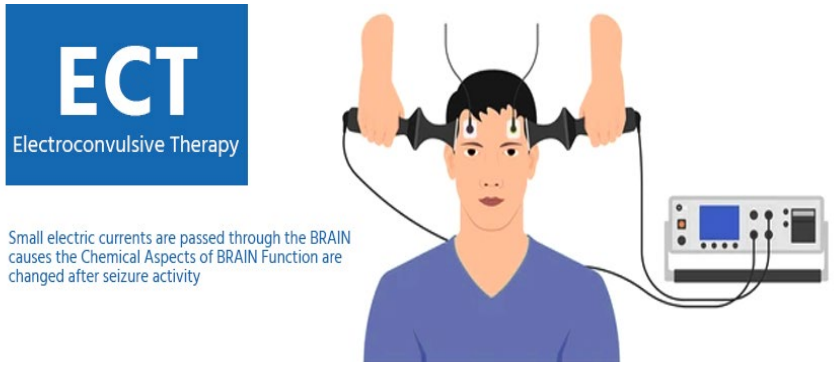
Interventions employed:

988

- 24/7 access to trained crisis counselors to help:
  - Thoughts of suicide
  - Mental health or substance use crisis
  - Any other kind of emotional distress
- People can call or text 988 or chat 988lifeline.org for themselves or another.
- Universal entry point—anywhere in US

https://mhttcnetwork.org/centers/global-mhttc/988-and-crisis-resources





SOMATIC THERAPIES

- Transcranial Magnetic Stimulation (TMS)
- Electroconvulsive Therapy (ECT)

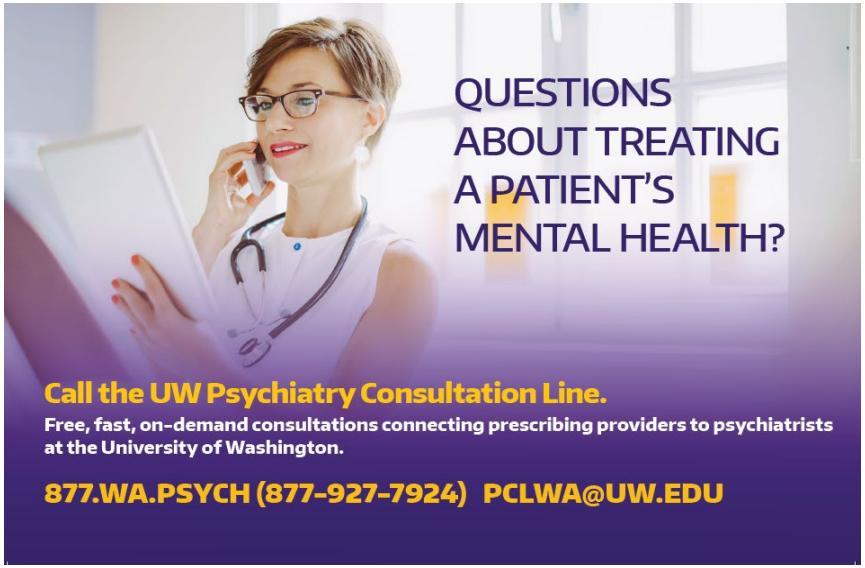
Garnatt SL, et al. Psychiatr Clin North Am 2018 Sep; 41(3): 419-431
Kirov G, et al. Br J Psychiatry 2021 Nov; 219(5): 594-597

CONCLUSIONS

- Only 30% of depressive episodes remit after first medication trial;
- More than 1/3 of depressive episodes fail more than 2 trials of antidepressant medications
  - most of these are not due to pharmacologic failure
- Switching and augmentation are equally effective, so individualize treatment;
- Risk assessment at every visit for depression

UW PSYCHIATRY CONSULTATION LINE (PCL)

- For prescribers caring for adults with mental health and/or substance use conditions



- Questions answered about:
  - ✓ Assessment
  - ✓ Diagnosis
  - ✓ Treatment planning
- Staffed by adult psychiatrists
- Available 24 hours a day, 7 days a week
- Free to the caller and the patient
- Written recommendations provided

AVAILABLE 24/7 | 877-927-7924 (877.WA.PSYCH) | PCLWA@UW.EDU

Partnership Access Line (PAL) and PAL for Moms

UW PSYCHIATRY AND ADDICTIONS CASE CONFERENCE (PACC)

https://ictp.uw.edu/programs/uw-pacc

- Free, weekly teleconference
- Connects community providers with psychiatrists, psychologists and addictions experts
- ECHO model
- Thursdays 12-1:30