Medication Management of Depression: The Care Manager Role

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Objectives

- Basic concepts of medication management
- Review of evidence-based medication management
- Review of commonly used antidepressants
- Managing side effects of antidepressants
- Identification of key drug-drug interactions

BASIC CONCEPTS OF MEDICATION MANAGEMENT

Do ADs work?

2018 Systematic Review & Meta-Analysis, The Lancet
(522 trials, 116,477 participants)

- Vast majority of trials funded by pharmaceutical industry
- Novelty bias
- Benefit for MDD in first 2mos of treatment
- ADs more effective than placebo

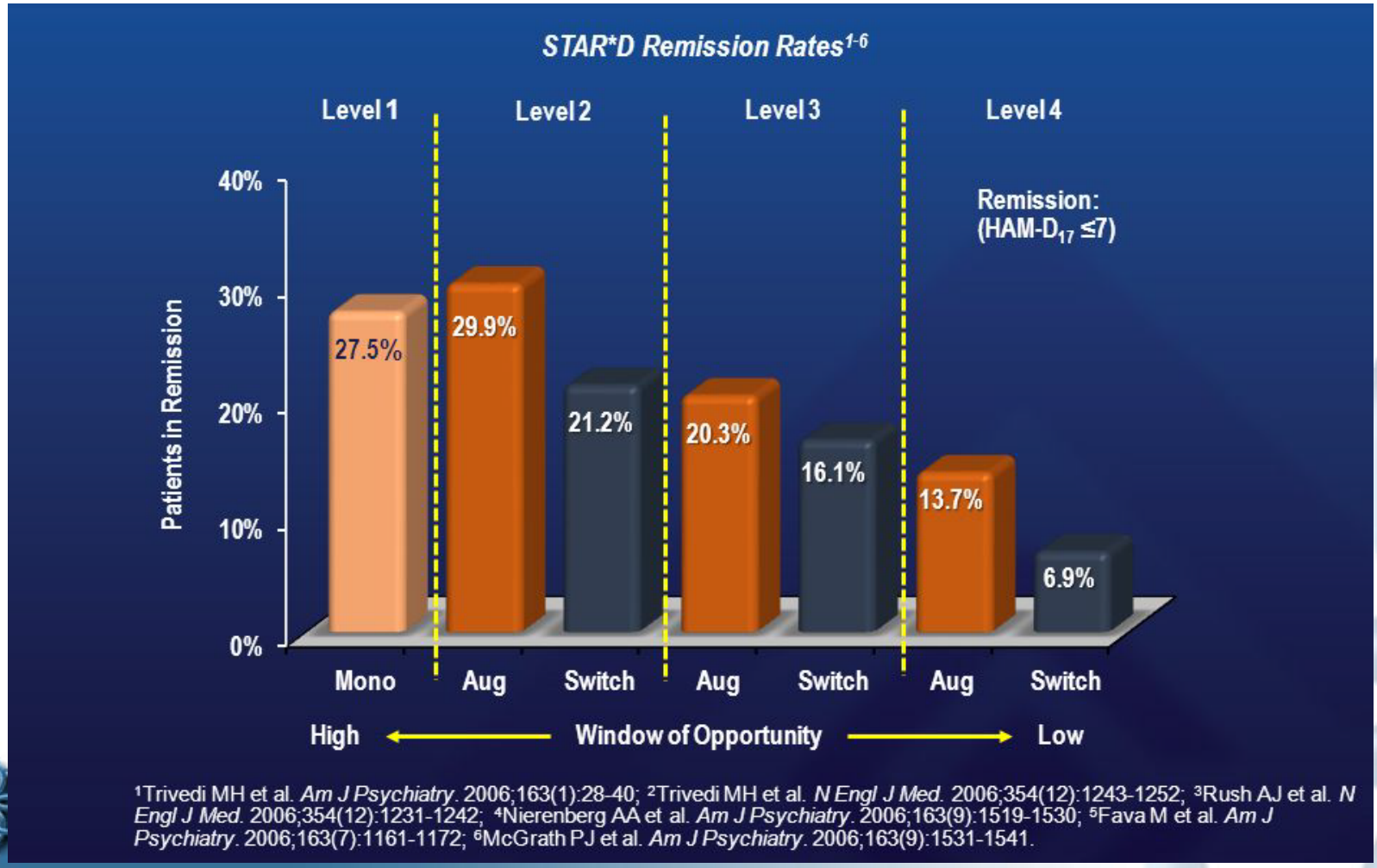
Cipriano, A, et al. Comparative efficacy and acceptability of 21 antidepressant drugs: a systematic review and network meta-analysis. *Lancet* 2018

Do ADs work?

STAR*D (funded by NIH):

Unclear if switching or augmenting is superior

Sequenced Treatment Alternatives to Relieve Depression (STAR*D) Study 2008



[1]Trivedi MH et al. *Am J Psychiatry*. 2006;163(1):28-40; [2]Trivedi MH et al. *N Engl J Med*. 2006;354(12):1243-1252; [3]Rush AJ et al. *N Engl J Med*. 2006;354(12):1231-1242; [4]Nierenberg AA et al. *Am J Psychiatry*. 2006;163(9):1519-1530; [5]Fava M et al. *Am J Psychiatry*. 2006;163(7):1161-1172; [6]McGrath PJ et al. *Am J Psychiatry*. 2006;163(9):1531-1541.

Consider medications if...

- PHQ-9 > 9
- Thoughts of self-harm or suicide
- Social, academic, occupational functioning are impaired
- History of MDE, self-harm, suicide attempt, hospitalization
- Therapy, lifestyle changes not helpful
- Co-occurring substance use

Choosing a Medication

- What has worked in the past
- What hasn't worked in the past
- Family members' experiences with medications
- Current medical illnesses
- Side effects (obesity, HTN, sedation, dosing)
- Age
- Cost
- Drug interactions
- Genetic testing results[1]
  - 12 genes, 55 medications
  - Improves remission rates by 50% in MDD
  - Improves response rates by 30% in MDD

[1]Greden, J. Combinatorial pharmacogenomics significantly improves response and remission for major depressive disorder: A double-blind, randomized control trial.

EVIDENCE-BASED MEDICATION MANAGEMENT

Treatment Goals

Response

- 50% decrease in symptoms (or PHQ-9 score)

Remission

- 6 months of no symptoms (PHQ-9 < 5)

Prevention

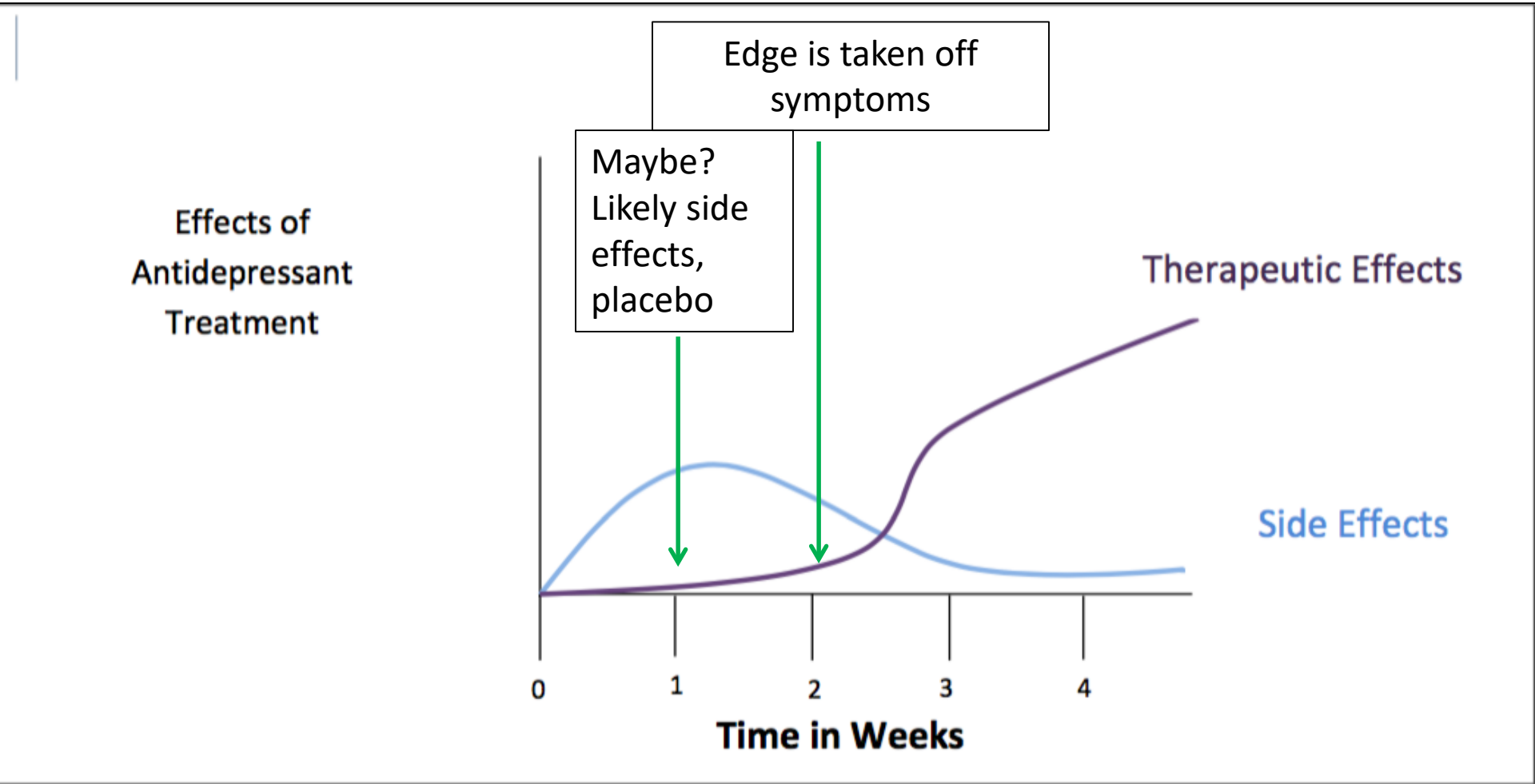
- Continue medications 6-12 months after sxs resolve

Maintenance

- If previous MDE off medications, recent/upcoming stressors

Course of Treatment

- Treat for at least 8 weeks
- Treat for 6-12 months after remission



Dosing

- For elderly patients, start low and go slow
- Use genetic testing as a guide
- Best to start low and achieve tolerability
- If partial response, increase dose every 4-6 weeks
- Once at max dose, switch or augment
- If no response after 4-6 weeks, consider switch or augmentation

Augmentation vs. Switching

- Head to head studies are not clear
- Abilify
- Seroquel
- Risperdal
- Zyprexa
- Lithium (especially if SI)
- Thyroid hormone T3 (levothyroxine)
- Wellbutrin
- TCA
- Not much evidence for Buspar

COMMONLY USED ANTIDEPRESSANTS

SSRIs

(Selective Serotonin Re-uptake Inhibitors)

- Prozac (fluoxetine), Zoloft (sertraline), Celexa (citalopram), Lexapro (escitalopram), Paxil (paroxetine), and Luvox (fluvoxamine)
- Safer in-overdose and tolerability
- Fluoxetine – least withdrawal (4-5 day half-life)
- Doses greater than 40 mg/day of citalopram and 20 mg/day of escitalopram not recommended due to increased QT prolongation risk (monitor with EKG, electrolytes)
- Doses greater than 20mg/day of citalopram and 10 mg/day of escitalopram not recommended in patients >60 y/o
- Hyponatremia in elderly
- Use lower dose of all SSRIs in hepatic impairment
- Dose adjustments usually not necessary in renal impairment

SNRIs

(Serotonin-Norepinephrine Reuptake Inhibitors)

- Effexor (venlafaxine), Pristiq (desvenlafaxine), Cymbalta (duloxetine), Fetzima (levomilnacipran)
- Withdrawal symptoms pronounced with venlafaxine (5 hour half-life)
- Avoid duloxetine in hepatic disease
- May increase blood pressure, monitor BP and pulse
- Good for patients that also have chronic neuropathic or musculoskeletal pain
- Use lower dose of all SNRIs with hepatic and renal impairment

NDRI

(Norepinephrine and Dopamine Reuptake Inhibitor)

Wellbutrin (bupropion)

- Less sexual side effects or weight gain
- Increased risk of seizure, caution use in patients with h/o prior seizures, eating disorders, head trauma/tumors, or alcohol abuse
- Helpful in smoking cessation
- Not good for anxiety, high caffeine intake
- May cause insomnia if taken too late in day
- Last dose no later than 4 pm
- Give 8 hrs between doses if given twice daily

TCAs

(Tricyclic Antidepressants)

- Older generation SNRIs
- Elavil (amitriptyline), Norpramin (desipramine), Pamelor (nortriptyline), Tofranil (imipramine), Sinequan (doxepin), Anafranil (clomipramine)
- High overdose risk due to cardiotoxicity
- Good for patients that also have chronic neuropathic or musculoskeletal pain, insomnia, or IBS
- Decreased tolerability compared to newer agents due to anticholinergic effects like dizziness, blurred vision, constipation, dry mouth, sedation, and weight gain
- SSRIs may increase concentration of TCAs

MAOIs
(Monoamine Oxidase inhibitors (MAOIs)

- Older antidepressants
- Ensam (selegiline), available in a transdermal patch, (Nardil) phenylzine, Parnate (tranylcypromine)
- Use is rare due to several diet and drug interactions that can result in hypertensive crisis (tyramine-containing foods and other serotonergic, noradrenergic or dopaminergic meds)
  - Wash out periods are essential when switching from another serotonergic to an MAOI

Mixed Serotonergics (Mixed 5-HT)

- Trazodone
  - Blocks serotonin reuptake and certain receptors
  - Mainly used as a hypnotic due to excessive sedation
  - Priapism
  - Sedation
  - Dizziness
  - Morning grogginess

- Viibryd (vilazodone)
  - New on market
  - SPARI - serotonin partial agonist and reuptake inhibitor
  - Expensive
  - No dosage adjustments in renal or hepatic impairment

Serotonergic and alpha 2-Adrenergic Antagonists

- Remeron (mirtazapine):
  - Increase serotonin and NE transmission (independent of reuptake)
  - 7.5 mg dose used for insomnia due to histaminergic effect at lower dose
  - ≥ 15 mg dose used for depression due to serotonergic and noradrenergic activity at higher doses
- Good for patients that need to gain weight (more weight gain with 7.5 mg dose)
- May reduce nausea
- Dose adjustment in renal and hepatic impairment

Multi-modal

Trintellix (vortioxetine):

- New on market
- Expensive
- Increases release of several different neurotransmitters (serotonin, norepinephrine, dopamine, glutamate, acetylcholine, and histamine) and reduces the release of GABA through 3 different modes of action
- May help with cognitive impairment
- No dosage adjustments in renal or hepatic impairment

MANAGING SIDE EFFECTS OF ANTIDEPRESSANTS

Side Effects

- Short term (2 weeks):
  - Headache, upset stomach/nausea, diarrhea, dizziness, anxiety, insomnia or fatigue usually occur immediately

- Longer term and dose dependent:
  - Sexual side effects, dry mouth, constipation, sweating, night sweats, weight gain

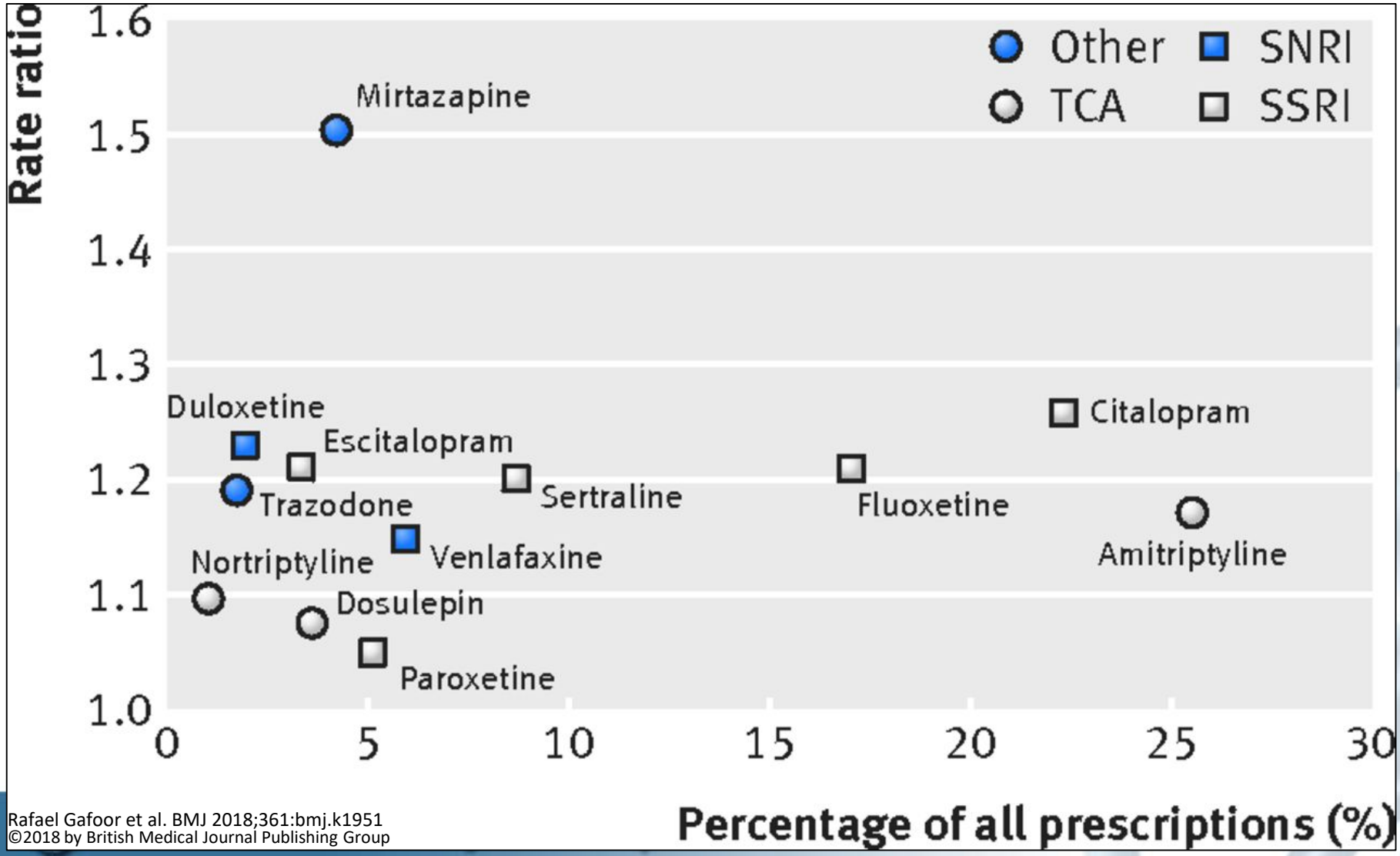
Suicidality with ADs

TABLE 3. **Revised Insert Guidance for Black Box Warning**

Age range (y)	Drug-placebo difference in number of cases of suicidality per 1000 patients treated
Drug-related increases	
<18	14 additional cases
18-24	5 additional cases
Drug-related decreases	
25-64	1 fewer case
≥65	6 fewer cases

Weight Gain

21% increased chance of ≥5% increase in body weight, 46% after 2 years



Rafael Gafoor et al. BMJ 2018;361:bmj.k1951

Preventing & Managing Side Effects

- Genetic testing
- Start at half the starting dose
- Divided doses
- Take with meals
- Avoid caffeine
- Increase exercise
- Switch timing of medication
- Continue same dose until resolution of side effects
- Choose wisely (h/o HTN, obesity, binge eating, anxiety, insomnia)
- Treating symptoms with another medication

Managing Medication Side Effects

Fatigue

- Take your medicine at bedtime
- Take short naps
- Exercise

Dizzy/ Lightheaded

- Get plenty of fluids
- Get up slowly when seated or lying down
- Ask your health care provider if wearing support hose will help

Dry mouth/eyes, constipation, water retention or fast heartbeat

- Drink liquids and sip water often
- Brush teeth two times a day and use sugarless gum or candy
- Eat more fiber
- Use eye drops (artificial tears)

Upset Stomach or Nausea

- Wait 1-2 weeks. Nausea often goes away on its own
- Take medicine with meals
- Ask your health care provider about adding another medicine like an antacid

Jitters, shakes or tremors

- Ask your health care provider if your depression can be managed with a lower dose of medicine

Restlessness, Anxiety and Agitation

- Ride a bike, jog or do other vigorous exercise
- Stay busy and focus on other things
- Use relaxation tools like muscle relaxation and deep breathing exercises
- Talk to your provider about changing medicines or adding a medicine to help you relax

Headache

- Take a pain relieve like acetaminophen (Tylenol or others) if your health care provider approves
- Ask your provider about taking a smaller dose

Insomnia (Hard Time Sleeping)

- Avoid caffeine (found in pop, coffee and chocolate)
- Take antidepressant in the morning
- Ask your health care provider about taking a medicine to help you sleep

Weight Gain

- Choose fruits, vegetables and whole grains and limit sweets, sugary drinks and fast foods
- Exercise 30 minutes each day
- Talk with your health care provider about changing medicines or doses

Problems with Sexual Function

- Ask your health care provider about changing your dose or your medicine
- Ask your provider about adding another medicine to treat sexual dysfunction

Missed Doses

- If miss 3 or more days of medication:
  - Withdrawal
  - No therapeutic effect
  - May need to restart with beginning dose
- Take medication at next scheduled time
  - Do not double up

Stopping Medications

- Taper to avoid withdrawal (worsening depression, suicidality, insomnia, anxiety, GI upset, headaches, dizziness, electrical zaps fatigue, sedation, diarrhea)
- The longer the treatment, the longer the taper
- The shorter the half life, the worse the withdrawal
  For example, to taper off Lexapro 10mg daily:
  - Week 1 – 7.5mg daily
  - Week 2 – 5mg daily
  - Week 3 – 2.5mg daily
  - Week 4 – 2.5mg every other day
  - Week 5 – stop

KEY DRUG-DRUG INTERACTIONS

Common Drug-Drug Interactions

Use Lexi-Comp!

- Serotonergic meds (triptans, TCAs, SSRI, SNRI, trazodone, buspirone) - Serotonin syndrome
  - More common when multiple agents combined
  - Dose dependent
  - Clonus, hyperthermia, and mental status changes
  - Relatively uncommon, but is still something to consider
- NSAIDs – GI bleeding
- Alcohol and drugs – CNS depression
- MAOIs – hypertensive crisis
- TCAs – increase in TCA serum concentration
- Tramadol – lower seizure threshold
- Certain antipsychotics – QTc prolongation

Common Drug-Drug Interactions

Use Lexi-Comp!

- Involve the cytochrome P450 enzymatic inhibition or induction
- If patient taking medication known to interact with antidepressant:
  - Start low
  - Go slow
  - Monitor for effect of interaction
  - Check a blood level (TCAs)

Drugs that may cause depression

- Alcohol, cannabis, cocaine
- Acne treatment: Accutane (Isotrentinoin)
- Anticonvulsants: Keppra (levetiracetan), Topamax (topiramete), Sabril (vigabatrin)
- Antimigraine agents: Triptans
- Benzodiazepines: Valium (diazepam), Xanax (alprazolam), Klonipin (clonazepam), Ativan (lorazepam)
- Cardiovascular medications: B-Blockers, Clonidine, methyldopa, reserpine
- Hormonal therapy: Gonadotropin-releasing hormone, oral contraceptives, steroids (prednisone), tamaxifen
- Immunologic agents: Interferons
- Smoking cessation drugs: Chantix (varenicline)

Questions?