Ten Principles for Practical Antidepressant Prescription
(and a Few Other Thoughts About Treating Depression)

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Disclosure

I have no financial interests or relationships to disclose.

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Axioms for Practical Antidepressant(AD) Rx

- All AD classes act by modulating monoamines.
- All AD classes show comparable efficacy.
- Each AD prescription is empirical, with an N of 1.
- AD's are NOT dx-specific; assess for comorbidities.
- Side effect profiles distinguish AD classes.
- Side effects can be good, bad, neither.
- Working with side effects :
  - Target specific depressive sx
  - minimize noxious effects
  - maximize beneficial effects

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Depression Treatment Options

- diagnostic clarification
- four management options
  - watchful waiting
  - psychopharmacology
  - psychotherapy referral
  - psychiatry referral
- focus of talk: ten prescribing principles

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Phenotype Does *Not* Equal Genotype

- 100 consecutive "depression" consults on an inpatient C/L service
- The development of the Eight D's Mnemonic
  - 29/100 met criteria for Major **D**epressive Disorder
  - 23/100: **D**emoralized
  - 15/100: **D**ifficult
  - 12/100: **D**rugged
  - 11/100: **D**elirious
  - 3/100: **D**isaffiliated
  - 2/100: **D**elusional
  - 2/100: **D**ulled
  - 3/100: **No** diagnosis
    - Bostwick & Rackley 2012

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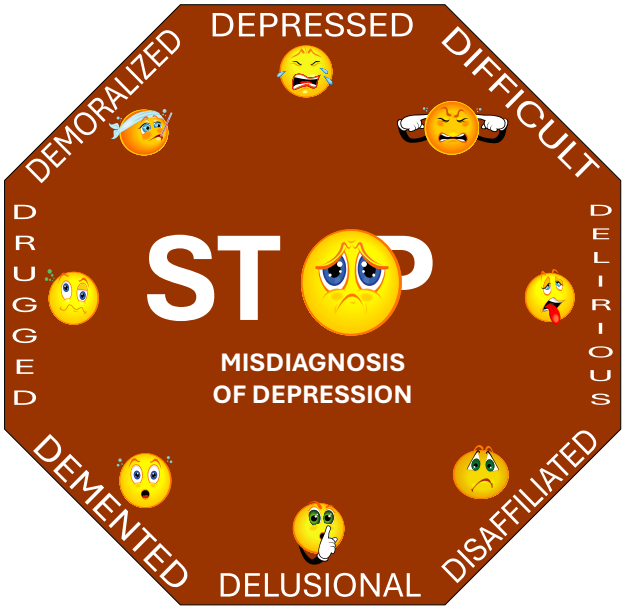

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DM is a 38 yo newly separated man in your primary care practice for 15 years. He is generally healthy, but you started a statin drug a decade ago due to his hyperlipidemia and hypertriglyceridemia. Family history is worrisome for severe cardiovascular disease. His paternal grandfather died at 43 from a massive heart attack, and his father died at 49 after a series of small heart attacks preceding the one that killed him. At his last appointment, DM mentioned concerns about erectile function, but you both chalked it up to marital discord. He has no previous psychiatric history, although he says his mother has been tense and anxious all his life and he has a sister with panic d/o.

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DM separated from his wife of nine years six weeks ago over disagreements about children: She wants them; he doesn't. Since the split, he has felt "down." He notices at work as a real estate agent that his concentration is off, his motivation to pursue new listings and show homes has flagged, and he worries about the listings he already has. He takes longer than usual to fall asleep from ruminating over how he could have managed the marital rift differently. On the other hand, his appetite is good, he's joined a health club, and he's lost a few pounds from regular workouts and "eating healthy". To his surprise, he has started dating a fellow "gym rat". He's enjoying the fling, both socially and sexually.

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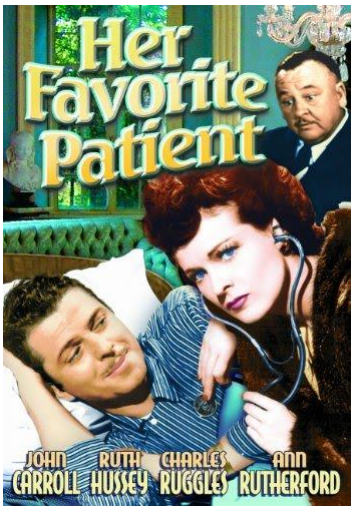
Wait Watchfully



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Principle 1: Wait Watchfully

- Don't rush to prescribe ADs for
  - depressive sx < than MD episode criteria
  - uncomplicated bereavement
  - adjustment disorder
- Symptoms may remit with
  - watchful waiting
  - supportive visits with physician

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DM returns a month later. Unfortunately, his symptoms have worsened. “I’m depressed, doc. I hate work I usually love, and I get even less done. I crave junk food, the more sugar the better. I’m exhausted. I wake up two hours before the alarm and can’t get back to sleep. I lie there thinking guilty thoughts about leaving my wife. I feel tense, grouchy, distracted. The only good thing is my love life. My new girlfriend seems not to notice, and we really have hit it off in the sack.”

You decide to start a trial of sertraline.

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Be Gingerly

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Principle 2: Start Low, Go Slow

- Initiate low AD dose, increase q 5-7 d.
- Titrate speed of increase to SE tolerability.
- Starting AD dose may be as little as 1/10th potential dose.
- Minimize polypharmacy.

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Disclose Possible Side Effects

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Principle 3: Disclose Potential Side Effects

- Inform patient of potential side effects.
- Discuss their management.
  - Early
    - Transient, bearable: continue AD
    - Noxious, unbearable: stop, reconsider
  - Late or persistent
    - Adjust dosage.
    - Add antidote or modulator.
    - Switch AD or AD class.

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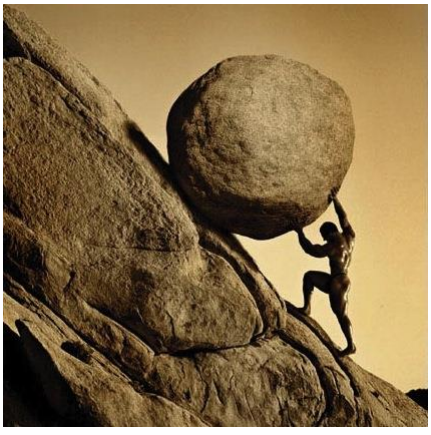
Be Realistic



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Principle 4: Set Realistic Expectations

- Adverse effects may occur prior to benefit.
- Recognizable benefit may take several weeks.
- Track specific target symptoms.
- Benefit may occur in small, incremental target symptom improvement.
- Remission may not occur with first – or even second or third – AD trial.

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You see DM back in three weeks. He is now up to 100 mg sertraline. You had warned him of common SSRI side effects. "I did get a little bit pukey at the beginning and I had a dull headache for a few days, but like you said, the side effects went away. My energy has picked up, I'm back at the gym, and I sold a house last week. I also still have trouble slowing my mind down enough when it's time for bed. The only thing I've noticed with my girlfriend is that it takes me longer than usual to get in the mood and sometimes I just can't climax.

You decide to add trazodone and sildenafil prn.

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Principle #5: Frame Side Effects as Neither Good nor Bad

- Elicit particular side effect concerns.
  - weight gain
  - changes in sleep
  - changes in sexual performance
- Select AD with potentially salutary SE profile.
  - few drug-drug interactions (e.g. citalopram)
  - weight-neutral AD (e.g. bupropion)
  - sedating AD (e.g. mirtazapine, TCA)
  - sex-neutral AD (e.g. bupropion)

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Be in Touch

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Principle 6: Schedule Frequent Follow-ups

- Make contact within 7-10 d of initiating AD.
  - Require phone check-in at minimum.
  - Focus on AD toleration rather than symptom alleviation.
  - Per Black Box Warning, SSRI-induced akathisia/agitation – particularly with SI – is a medical emergency.
- Encourage patients to call with any concerns.
- adherence with 3 visits/first 3 months.

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Two months later, DM is feeling "more or less like my old self." But he has some concerns he wants to discuss. He has gained back the weight he lost, plus another 10 pounds. He stopped the trazodone which did help him get to sleep "because I was waking up with what felt like a hangover every morning that didn't wear off until noon." Since using the sildenafil, his erections have been more reliable and firmer, even as his libido continues to flag. His girlfriend is understanding, but "I want it to be like it used to be."

Given his weight gain, sleep issues, and sexual function concerns, you decide to taper the sertraline and initiate bupropion.

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Be Prepared

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Principle 7: Try Antidotes to Counter Side Effects

- anxiolytics during early treatment to increase adherence
- trazodone, sleep agents during early treatment to increase adherence
- trazodone, sleep agents to temper AD-induced insomnia
- PDE-5 inhibitors (e.g. sildenafil) to combat sexual dysfunction

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Principle 8: Avoid AD Discontinuation Syndrome

- AD discontinuation symptoms can be
  - neuropsychiatric
  - emotional
  - Physical
- Taper when discontinuing ADs
  - Reduce dose by 25-50% per week.
  - Taper more slowly
    - the longer the patient has taken the AD.
    - the shorter the AD's half-life.

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DM has tolerated the bupropion well. He uses the trazodone 1-2 nights a week "when I can't sleep and I don't have to be alert early in the morning." He has experimented with sildenafil and finds that 100 mg "does the job." He says he is liking his girlfriend more and more and would hate to lose her, "but I know I'm on the rebound, and I'm not sure it's love." He's afraid he'll sabotage the relationship if he's not careful. On nights when he can't fall asleep, he says it's because, "I can't stop worrying about how this relationship thing is going too fast."

You decide to make a psychotherapy referral.

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Combos Are Better

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Principle 9: Pharmacotherapy and Psychotherapy Are Synergistic

- Pharmacotx for severe anhedonia, overwhelming neurovegetative sx, incapacitating anxiety
- Psychotx for prominent negativistic thinking; catastrophizing; assumptions perpetuating dysphoria, helplessness
- Combination therapy is more effective, more rapid than either therapy alone.
- Pharmacotx in severe depression may reduce cognitive dysfxn of severe depression, rendering psychotx more effective.

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Three months later, DM is doing well. At six months, however, it's another story. He reports two months ago having chest pain severe enough that he went to the ED. Myocardial ischemia was diagnosed; he was admitted, and three stents were placed. The cardiologist stopped bupropion and trazodone while he was an inpatient and no one at rehab thought to restart them. He was also told to stop using sildenafil due to potential interactions with prn nitroglycerin. In the weeks since, his depressive symptoms have roared back. He sums things up thus: "Not only is my marriage on the rocks but now my body's quitting on me, too!"

You decide to seek psychiatric consultation.

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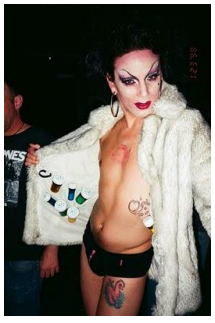
If Treatment Resistance, Consider Referral

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10) Consider Psychiatric Referral If Patient Has:

- minimal or no response to adequate (>8 wk) AD trial(s)
- labile or recurrent illness course
- adverse effects without sx relief
- complex medical or psychiatric comorbidities
- complex psychotropic regimen/polypharmacy
- active suicidality
- simultaneous manic, depressive sx (“mixed state”)
- hx suggestive of past mania
- strong fam hx psych d/o, substance abuse

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Closing Thoughts About New Treatments

- Copycat drugs:
  - SSRIs: citalopram, escitalopram, paroxetine, fluoxetine, sertraline, vortioxetine, vilazodone
  - SNRIs: duloxetine, venlafaxine, levomilnacipran, desvenlafaxine
- Restricted or investigational drugs:
  - NMDA antagonist: intranasal esketamine
    - Spravato REMS
  - GABA-A Receptor Modulator: IV brexanolone
    - Zulresso REMS
  - psychedelics/hallucinogens

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STAR*D: AD's Are Not Panaceas

- STAR*D is the largest, most consequential AD study ever conducted.
- Remission rather than response was tx goal
- If first tx failed, tx was switched or augmented.
- After 2 adequate (12-14 wks each) trials, remission likelihood decreased significantly.
- With persistent, vigorous tx, remission achieved.
  - 27.3% after Step 1 (but 48.3% dropped out)
  - 23.8% more on Step 2 (but 52.0% dropped out)
  - 16.2% more on Step 3 (but 65.6% dropped out)
- Overall: ~ 1/3rd remitted, but > 1/2 dropped out.

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Evidence-based Psychotherapies

- ACT-D: Acceptance & Commitment Therapy
- Behavioral Activation
- CBT: Cognitive Behavioral Therapy
  - adaptations for insomnia, depression, substance use d/o's
- DBT: Dialectical Behavioral Therapy
- IPT: Interpersonal Therapy
- MET: Motivational Enhancement Therapy
- PST: Problem-Solving Therapy
- Etc.

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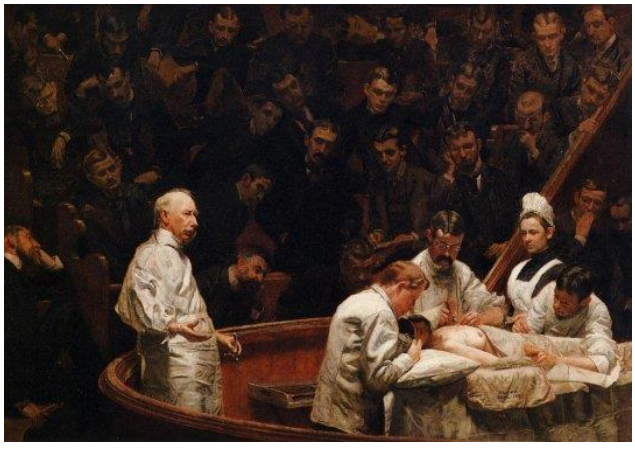

Thanks!

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Bibliography

- Bostwick JM. A generalist's guide to treating patients with depression with an emphasis on using side effects to tailor antidepressant therapy. *Mayo Clin Proc* 2010; 85:538-550.