Treatment-Resistant Depression (and how to obtain remission)

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What is ‘Treatment-Resistant Depression?’

- Treatment-resistant depression (TRD) typically refers to inadequate response to ≥1 antidepressant trial of *adequate dose and duration*
- At least 6-8 weeks of treatment
  - even up to 10 weeks
- Dose greater than a ‘starting’ one
  - e.g. fluoxetine 30-40mg/d; bupropion 300-400mg/d

STAR*D Study Overview

- N~4000 patients
- Level 1-Citalopram
- Level 2-Switch to SERT, BUP, VFX, CBT
  OR Augment with BUP, BUSP, CBT
- Level 2a-CBT nonresponders switch to VFX, BUP
- Level 3-Level 2/2a nonresponders Switch to MIRT, NTP
  OR Augment with LI, THYR
- Level 4-Switch to TRANYLCYP, MIRT+VFX

What STAR*D Showed

- 65% did not achieve remission
- Among remitters, up to 50% continued to experience up to two residual symptoms of depression (Fava et al, 2006)
- Increased risk of relapse, recurrence, and poor psychosocial functioning (Fava et al, 2006)
- Symptoms can involve cognitive and social impairment
  - Social impairment may improve with treatment
  - Cognitive impairment may remain (Airaksinen et al, 2006)

Can we Predict Chances of Remission?

- Predictors of LOWER remission rates
  - Longer current episodes
  - More psychiatric comorbidity
    - especially anxiety or drug abuse
  - More medical comorbidity
  - Lower baseline function and quality of life
- 40% of remitters required ≥8 weeks of treatment
- After two failed treatment trials, chances of remission decrease significantly (STAR*D)

How do we Obtain Remission?

- Often requires aggressive and creative solutions
  - High doses of antidepressants
  - Combinations of antidepressants
  - Augmentation with other agents
  - Longer treatment duration
  - Addition of psychotherapy
  - Somatic therapies (Shelton et al. 2010)
    - Electroconvulsive Therapy (ECT)
    - Transcranial Magnetic Stimulation (TMS)
- Preferably carried out by a psychiatrist

Strategies for Obtaining Remission

Optimize…?
Augment…?
Switch…?
Combine…?

Case Vignette: Bill

- 35 year-old white male, good general health
- Presents with first depressive episode
- You start him on fluoxetine 20mg/day
- After 8 weeks, he reports only a partial improvement
- **What would you do?**

A. Increase dose to 30-40mg daily

B. Switch to bupropion

C. Add bupropion to boost effect of fluoxetine

D. Allow him to continue on this dose for another month

Optimizing Doses

- Historically, goal has been to attain response at the lowest dose necessary
- Avoids side effects, minimizes risk of interactions
- May result in residual symptoms, non-remission
- Remission may require higher doses, longer duration
- Aim for *adequate trials*:
  - At least 6-8 weeks of treatment, even up to 10 weeks
  - A dose greater than a ‘starting’ one (e.g. fluoxetine 30-40mg/day; bupropion 300-400mg/day)
  - Higher dose may provide greater benefit

Bill (cont'd)

- You increase the fluoxetine dose to 40mg daily
- After 6 more weeks, Bill reports no further gains
- He complains of mild sedation and some erectile dysfunction
- **What would you do?**

A. Switch to bupropion
B. Augment with lithium
C. Combine with bupropion
D. Combine with citalopram

Switching Antidepressants

- Switch usually within or between AD classes
- Advantages over combination or augmentation
  - Avoidance of polypharmacy
  - Fewer treatment-emergent adverse events
  - Lower risk of interactions
  - Cheaper
- Disadvantages
  - Partial benefit from initial treatment might be lost
  - Monotherapy switches have shown limited effectiveness in achieving remission (Shelton et al, 2010)
- No advantage for any particular agent

Combination Therapy

- Uses complementarity of mechanisms of action
- SSRI plus bupropion: among most popular
- SSRI plus TCA: still fairly common
- "California Rocket Fuel" (Stephen Stahl)
  - Mirtazapine plus venlafaxine (or other SNRI)
  - Theoretical synergy
  - Norepinephrine reuptake blockade (NE boost)
  - Serotonin reuptake blockade (5HT boost)
  - Alpha-2 antagonism (5HT, NE boost)
  - 5HT2A / 5HT2C antagonism (5HT, NE boost)
  - Double boost of dopamine (5HT2A and 5HT2C antag.)

Augmentation Therapy

- Also uses complementary mechanisms
- Usually involves adding a medication not specifically approved or typically used as monotherapy for unipolar depression
- Thyroid hormone, Lithium
  - Well studied, not often used
- Atypical antipsychotics: aripiprazole, olanzapine
  - Growing in popularity
- Stimulants: including modafinil
- Antiparkinsonian agents: pramipexole
- Anxiolytics: buspirone

Combination and Augmentation vs. Switching

- Advantages of combination/augmentation
  - Recommended if partial response was achieved with the original antidepressant
  - Allows targeting of different symptoms (e.g. adding a sedating second agent if insomnia is a problem)
- Disadvantages
  - More complicated regimen (some clinicians may be uneasy)
  - Greater chance of adverse events and interactions
  - Higher cost
  - Too much patient dependence on medication?
- No advantage for any particular agent (Shelton et al, 2010)

What Did STAR*D Show?

- Difficult to compare benefits of switching versus combining in STAR*D Study (Gaynes et al, 2010)
- Patients *chose* whether to switch from citalopram to another treatment or to add another treatment at level 2
- Patient groups were therefore not equivalent at randomization at level 2
  - Patients who benefited from and tolerated citalopram preferred augmentation
  - Patients who benefited little or could not tolerate citalopram preferred switching
  - Augmentation group was therefore somewhat less depressed than those who switched
- Whether augmentation is better even if the initial treatment is minimally effective could not be evaluated in STAR*D

Proposed Approach

- Evaluate factors that may contribute to treatment nonresponse (e.g. comorbid medical and psychiatric conditions)
- Add therapeutic ingredients as long as they are needed (Rafanelli et al, 2007)
- Use any of the four classical strategies for enhancing antidepressant efficacy
  - Optimization, switching, augmentation, combination (Berlim et al, 2006)

Other Strategies

- Use of polypharmacy *from the beginning* of treatment, bypassing monotherapy altogether (Thase, 2009)
  - Controversial, due to greater risk of adverse effects and interactions
  - Risk of giving unnecessary medication
- Combined therapies, such as antidepressants plus psychotherapy are also commonly used
- Somatic therapies

STAR*D Strategies for Combination and Augmentation

- Combinations
  - Venlafaxine plus mirtazapine
  - Citalopram plus bupropion
- Augmentation
  - Citalopram plus buspirone
  - Citalopram plus CBT
  - Citalopram plus lithium or T3
  - (Sertraline or bupropion or venlafaxine) plus Li or T3
- All effective, no clear-cut "winner" (Gaynes et al, 2008)

Other Combinations and Augmentation

- Other strategies supported in the literature
  - SSRIs plus desipramine, clomipramine, eszopiclone, pindolol, buspirone, modafinil, thyroid, olanzapine, aripiprazole, pramipexole, lisdexamphetamine, celecoxib, topiramate, pregabalin, lamotrigine, d-cycloserine, riluzole, memantine, minocycline, scopolamine, ketamine, mirtazapine
  - Mirtazapine plus bupropion
  - Imipramine plus amantadine
  - Buspirone plus melatonin

Bill (cont'd)

- You add bupropion SR at 150mg daily
  - Rationale: proven agent; activating, stimulant-like (for sedation); shown to reverse SSRI-induced sexual dysfunction
- After 6 weeks, Bill is feeling almost normal; has more energy; sexual function has improved significantly
- **What would you recommend next?**

A. Discontinue both medications

B. Discontinue one medication

C. Decrease dose of one medication

D. Continue regimen for 6-12 months

Recurrence of Depression

- Depression can be recurrent
  - More likely with more episodes
- Bill is in his first episode
  - Good chance that he may eventually be able to discontinue or reduce medications
- But risk of recurrence is higher if you discontinue or reduce antidepressants too early
- Best to continue regimen for at least 6-12 months
- Monitor for emergence of side effects

Bill (cont'd)

- 12 months later, Bill continues well
- He expresses concerns about being on so much medication
- He is strongly interested in trying to cut down or stop the medications
- **What would you do?**

A. Discontinue one medication

B. Discontinue both medications

C. Decrease doses of both medications and observe

D. Decrease one medication and add psychotherapy

Psychotherapy

- Psychotherapy and pharmacotherapy may target different sections of the cortical-limbic pathway
- Adjunctive psychotherapy in acute depression may provide a modest advantage
- Targets residual symptoms and symptoms associated with relapse
  - Irritability, guilt, hopelessness, negativity, low self-esteem
  - Promotes coping skills, healthy cognitive changes
  - May be viable alternative to maintenance pharmacotherapy (GA Fava et al, 2006); data not consistent
  - Combined pharmaco-psychotherapy may prevent or delay relapse/recurrence (Petersen, 2006)

What Type of Psychotherapy?

- Cognitive Behavioral Therapy (CBT)
  - Best studied
  - Goal-oriented; time-limited; modifies erroneous cognitions that affect behavior
  - CBT + antidepressants is a common combination
  - No difference between cognitive therapy (either as a switch or as augmentation) and medication (as a switch or as augmentation)
  - Adding another drug was more rapidly effective than adding cognitive therapy
  - Switching to cognitive therapy was better tolerated than switching to a different antidepressant

Other Types of Psychotherapy

- Dialectical Behavior Therapy (DBT)
  - For affective dysregulation, Borderline PD; time-limited
- Interpersonal therapy
  - Focus on building interpersonal skills
- Psychodynamic therapy
  - Focus on impact of early experiences; long-term
- Mind-body interventions
  - Often for symptomatic reduction, stress control
- Motivational interviewing
  - Encourage behavior change by examining discrepancies between patient's desires and actual situation; resolve ambivalence

Natural Remedies

- Less well studied than standard agents
  - Appealing in part due to low side effect burden
  - Growing support in the literature, particularly for antidepressants such as St John's Wort, Omega-3, and SAMe
  - These should always be used with caution, as there may be unknown risks

Natural Remedies (cont'd)

- Omega-3 Fatty Acids (Mischoulon et al, 2008, 2009, 2014 in press; Freeman et al, 2006)
  - For monotherapy or augmentation
  - About 1000mg/day of EPA/DHA preparation
- SAMe (S-adenosyl methionine) (Alpert et al, 2004; Papakostas et al, 2010; Mischoulon et al, 2014)
  - For monotherapy or augmentation
  - Doses of 400-1600mg/day
- Methylfolate (Papakostas et al, 2012)
  - Dosed at 15mg/day augmentation
- Creatine (Lyoo et al, 2012)
  - Dosed at 5g/day augmentation in women

Natural Remedies (cont'd)

- St John's Wort (Hypericum Study Group, 2002; Fava et al, 2005)
  - Dosed at 900-1800mg/day
  - Interacts with other meds; use with care
  - Do not combine with SSRIs (serotonin syndrome)

- Ginkgo Biloba (Amri et al, 2008)
  - Dosed at 120-240mg/day
  - cognitive benefits in elderly and in young and healthy populations
  - Avoid in patients at risk of bleeding

Somatic Therapies

- Approved Therapies
  - Electro Convulsive Therapy (ECT)
    - After multiple failed trials, severe depression, need for rapid response; often requires AD for maintenance
  - Vagal Nerve Stimulation (VNS)
    - After four prior treatment failures
    - Requires prolonged use for benefits (1+ year)
  - Transcranial Magnetic Stimulation (TMS)
    - After failing one adequate trial of an antidepressant
- Experimental Therapies
  - Deep Brain Stimulation (DBS)
  - Psychosurgery

(Shelton et al, 2010)

Summary

- Partial response and residual symptoms are common
- Medication combinations can maximize improvement
  - But may increase side effects
  - Natural therapies may minimize side effects
- Minimizing side-effect burden and residual symptoms may improve standard of care for mood disorders
- Psychotherapies may be an excellent adjunct
  - In parallel or in sequence
  - Select right therapy for right patient
- Multimodal care requires good coordination and communication between different treaters

Recommendations

- Aim for remission rather than response
- Remission gives better function and prognosis
- With persistent and vigorous treatment, most patients will enter remission (Gaynes et al, 2008)
  - ~33% after one step
  - ~50% after two steps
  - ~60% after three steps
  - ~70% after four steps

…assuming patients stay in treatment!

Recommendations (cont'd)

- Give maximal but tolerable doses for at least 8 weeks before deciding that an intervention has failed
- Consider using measurement-based care to better assess response to treatment (e.g. QIDS scale)
- Consult clinical guidelines and clinical trials that include remission as a primary outcome measure (Trivedi, 2009)
- Areas to be further addressed (Berlim et al, 2006)
  - Validity of diagnostic criteria
  - Evaluation of reliable predictors of treatment outcome
  - Development of novel therapeutic strategies