"When I die, I hope it's in a meeting. The transition from life to death will be barely perceptible."

Richard Balon
TREATMENT RESISTANT ANXIETY: DEFINITION, RISK FACTORS AND TREATMENT CHALLENGES

Peter P. Roy-Byrne M.D.
Professor
Department of Psychiatry
University of Washington School of Medicine
Faculty Disclosure

• Dr. Roy-Byrne has in the past 3 years:
  – Received research support from
    • National Institute of Mental Health
    • National Institute of Drug Abuse
  – Been a paid (stock options) consultant for
    • Valant Medical Systems (Behavioral Health EMR Company)
  – Been paid as Editor-in-Chief for
    • *Depression and Anxiety* (Wiley Press)
    • *Up-to-Date Psychiatry*
    • *Journal Watch Psychiatry* (Mass Medical Publishing)
THE FUNDAMENTAL TENSION

• “Evidence-Based Practice”---Data from placebo-controlled RCTs (control for variability in patient and care process characteristics) show what “works”. But Placebo controlled trials will NOT detect true therapeutic effects in a tiny proportion of the group being studied i.e. <10%

• “Practice-Based Evidence”—Information from clinical practice experience (no control for the “clinicians illusion” where once something works, you do it more and more, with an evident and communicated bias that promotes placebo responses). Some “ineffective” treatments COULD work for a given patient, but should NOT be tried until more effective ones have been given a chance.
TREATMENT RESISTANT ANXIETY

- Definition and Prevalence
- Determinants
  - “Pseudo-Resistance”
  - True Treatment Resistance
- Treatment Approaches
TREATMENT-RESISTANT ANXIETY
DEFINITION & PREVALENCE

• Includes failure to remit (60%), or respond (30%), or respond persistently i.e. not relapse (10-30% over 1-10 years)

• So 70% cases may be “refractory” at some point

• Since each syndrome has multiple components, need to consider all relevant response dimensions (i.e. for some, “response” may be limited to one domain and so they could be “non-responders”)

• Panic as the most complex example with multiple domains
  – Panic frequency & intensity
  – Phobic avoidance
  – Panic sensation avoidance
  – Anticipatory anxiety
  – Work & Social
  – Disability
DETERMINANTS OF TREATMENT-RESISTANT ANXIETY

- Pseudo-Resistance—lack of adequate treatment (clinician driven) or failure to adhere to treatment (patient driven)
- True Treatment Resistance—failure to respond due to wrong diagnosis, complicating comorbidities, or exogenous anxiogenic factors
PSEUDO-RESISTANCE: CLINICIAN AND PATIENT CONTRIBUTIONS

• Clinician factors (“error”) a more common contributor to psychotherapy pseudo-resistance

• Patient factors (adherence), a more common contributor to medication pseudo-resistance

• This reflects the relative difficulty of delivering good psychotherapy vs good pharmacotherapy (concept of “robustness”)
ANXIETY TREATMENT Efficacy

• Medication and CBT equally effective for: Panic, GAD, SAD
• CBT more effective than medication for OCD
• Medication and CBT probably equivalent for PTSD (Zoellner and Feeny study results pending)
ASSURING ADEQUATE MEDICATION TREATMENT FOR ANXIETY

- SSRI, SNRI, probably MAOIs for all four disorders; only SSRI or CMI for OCD
- Bzs do not work for OCD PTSD
- TCAs do not work for SAD or OCD
- Buspirone and Trazadone work ONLY for GAD
- Beta-Blockers work ONLY for performance SAD and at a weak level for GAD
- Bupropion does not work for ANY anxiety disorder (but agitated depression may respond very well!)
ASSURING ADEQUATE MEDICATION TREATMENT FOR ANXIETY: DURATION IS CRUCIAL!

- Anxiety requires a longer time to respond than depression—get dose up during same time
- Acute treatment takes 8-12 weeks
- Even after this, because of the disabling behavioral effects of anxiety, further benefit can accrue over the next 3 months
- This is the biggest challenge for clinicians and requires psychotherapeutic expertise i.e. to help patient be patient!
Paroxetine Treatment of Social Anxiety Disorder

CGI Responders (%)

Week

Paroxetine (N=94)
Placebo (N=93)

*p ≤ 0.001 vs. placebo Adapted with permission from Stein et al. JAMA. 1998;280:708
Continuation Phase Outcome with Sertraline Treatment of PTSD Based on Acute Phase Response Category

Responder = > 30% decrease CAPS and CGI-S = 1 or 2
ASSURING ADEQUATE PSYCHOTHERAPY FOR ANXIETY

• CBT (various forms and versions) is the only treatment that works for all five disorders (but PE better for PTSD and ERP better for OCD)
• Mindfulness (GAD), psychodynamic psychotherapy (Panic, GAD, SAD) and IPT (PTSD) have some efficacy but far fewer studies and testing often done in mixed diagnostic groups
• Psychotherapy is much harder to deliver adequately than medication (more expertise is required), and any non-CBT treatment is harder to deliver adequately than CBT
Psychodynamic Therapy for Panic

Milrod B et al., Am J Psychiatry 2007
PSYCHODYNAMIC PSYCHOTHERAPY FOR SAD: NOT EQUAL TO CBT

Remission CBT, PD, WL = 36%, 26%, 9% (CBT > PD > WL)
Response CBT, PD, WL = 60%, 52%, 15% (CBT = PD > WL)

Leichsenring et al 2013, Am J Psychiatry
CBT DELIVERY FAILURE

- Most common is failure to progress to exposure due to clinician discomfort or inadequate training
- Sometimes failure to focus sufficiently on cognitive themes
PATIENT CONTRIBUTORS TO PSEUDO-RESISTANCE
“Woah—way too much information.”
TREATMENT INTOLERANCE: HIGH RATE OF NEGATIVE PLACEBO RESPONSE IN ANXIOUS PATIENTS

Loebel et al., 1986
CBT ATTENUATES PANIC DURING BZ DISCONTINUATION

Otto et al., 1993
CBT Increases Medication Tolerability

CBT Blunts Perception of Side Effects

- Imipramine only (n = 83)
- Imipramine plus CBT (n = 65)
- Placebo (n = 24)

Severity of side effects (rated 0 to 3)

MEDICATION TREATMENT INTOlersANCE: APPROACHES

- Education and patient preparation (Explanatory model, past experience, time course)
- Baseline ratings of anxiety (=side effects)
- Close (2x weekly) monitoring by phone or message for first few weeks
- CBT Techniques--exposure with low dose, slow titration, side effects reframing consistent with patients own model of illness (most important)
TREATMENT NON-ADHERENCE IN ANXIETY DISORDERS

- Hypersensitivity to Medication (especially in Panic)
- “Normalizing attitudes” about anxiety— attribution to stress (Panic and GAD), to personality (SAD), to trauma (PTSD)
- Negative Beliefs about Treatment Efficacy— sometimes related to prior adverse personal or familial experiences with medication or psychotherapy
- Fear of Medication “Dependence” (sometimes confused also with fears of medication “addiction”)
- Recovery and Acute Illness Model (late non-adherence)
- Structural and other barriers to treatments— low income, culture and ethnicity
Panic Patients with Negative Beliefs About Treatment Efficacy Drop Out More Often

NOT GETTING PREFERRED TREATMENT REDUCES ADHERENCE

<table>
<thead>
<tr>
<th></th>
<th>PE (n = 116)</th>
<th>Sertraline (n = 84)</th>
<th>Cohen’s d (preference)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prefer PE</strong></td>
<td><strong>67</strong> (70.5%)</td>
<td><strong>10 (47.6%)</strong></td>
<td><strong>42 (77.8%)</strong></td>
</tr>
<tr>
<td><strong>Prefer SER</strong></td>
<td><strong>42 (77.8%)</strong></td>
<td><strong>15 (50.0%)</strong></td>
<td><strong>7.97 (3.28)</strong></td>
</tr>
<tr>
<td><strong>Cohen’s d</strong></td>
<td><strong>144.20 (66.46)</strong></td>
<td><strong>62.03 (69.63)</strong></td>
<td>**1.18 *****</td>
</tr>
<tr>
<td><strong>PE: In vivo</strong></td>
<td><strong>19.52 (11.71)</strong></td>
<td><strong>13.57 (14.56)</strong></td>
<td><strong>--</strong></td>
</tr>
<tr>
<td>Exposure Hwk</td>
<td><strong>15.21 (9.71)</strong></td>
<td><strong>10.19 (10.73)</strong></td>
<td><strong>--</strong></td>
</tr>
</tbody>
</table>

*p < .05, **p < .005, ***p < .0005, two tailed.*
TREATMENT RESISTANCE: KEY FACTORS

• Exogenous Factors
• Unrecognized Medical Illness
• Wrong “Primary” Diagnosis—Somatic Symptom Disorder, BP, AHDD, Substance Abuse
TREATMENT RESISTANCE: ROLE OF EXOGENOUS ANXIOGENIC FACTORS

• Health Habits
  – Caffeine
  – Alcohol
  – OTC Cold Preparations
  – Lack of Exercise/Deconditioning
  – Sleep Deprivation
  – Nicotine (panic risk)

• Life Events/Stress
  – Acute
  – Chronic (low SES; lack of social support)
  – Systems Readjustment (Marital)

• Substance Use
  – Marijuana
  – Alcohol
Differential Anxiety Response to Sleep Deprivation

Depression

Panic Disorder

Roy-Byrne et al 1986
CHRONIC LIFE STRESSORS: EFFECT ON ANTI-PANIC TREATMENT

(Wade et al., 1993)
DISTURBED SPOUSE AND FAMILY RELATIONSHIPS PREDICT LACK OF REMISSION IN GAD

Yonkers et al 2000
POORER SSRI RESPONSE IN LOW INCOME PANIC DISORDER PATIENTS

Roy-Byrne et al 2003
POORER SOCIAL SUPPORT AND MORE LIFE EVENTS PREDICTS PTSD CHRONICITY

Udwin et al 2000

N=217

P<.00

P<.01
**Table 2. Relationship Between Marijuana Use and Clinical Outcomes at 4-Month Follow-Up**

<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>PTSD symptom severity (SF-MISS)</td>
<td>37.71 (0.228)</td>
<td>36.64 (0.385)</td>
<td>38.92 (0.383)</td>
<td>39.67 (0.226)</td>
<td>21.47</td>
<td>&lt;.0001</td>
<td>3, 4 &gt; 1, 2</td>
</tr>
<tr>
<td>Violence</td>
<td>0.87 (0.041)</td>
<td>0.76 (0.068)</td>
<td>0.93 (0.068)</td>
<td>1.25 (0.040)</td>
<td>21.28</td>
<td>&lt;.0001</td>
<td>4 &gt; 1, 2, 3</td>
</tr>
<tr>
<td>Alcohol abuse (ASI)</td>
<td>0.096 (0.007)</td>
<td>0.079 (0.011)</td>
<td>0.129 (0.011)</td>
<td>0.229 (0.006)</td>
<td>88.51</td>
<td>&lt;.0001</td>
<td>4 &gt; 1, 2, 3; 3 &gt; 1, 2</td>
</tr>
<tr>
<td>Drug abuse (ASI)</td>
<td>0.037 (0.0033)</td>
<td>0.034 (0.0056)</td>
<td>0.128 (0.0056)</td>
<td>0.130 (0.0033)</td>
<td>176.26</td>
<td>&lt;.0001</td>
<td>3, 4 &gt; 1, 2</td>
</tr>
<tr>
<td>Employment status (ASI)</td>
<td>0.578 (0.007)</td>
<td>0.575 (0.011)</td>
<td>0.594 (0.011)</td>
<td>0.577 (0.007)</td>
<td>0.66</td>
<td>.5752</td>
<td></td>
</tr>
</tbody>
</table>

aData presented as least-squares mean (SE), covarying for marital status, age, race, history of incarceration, waiting list status, psychosis, chronic medical problems, war zone service, length of stay, expulsion from treatment, and baseline measures of violence, PTSD, drug and alcohol abuse, and employment.

*P < .01.

Abbreviations: ASI = Addiction Severity Index; PTSD = posttraumatic stress disorder; SF-MISS = Mississippi Scale for Combat-Related PTSD, Short Form
“I was on hormone replacement for two years before I realized that what I really needed was Steve replacement.”
ANXIETY AND UNRECOGNIZED MEDICAL ILLNESS

• In practice this is not very common, but failure to recognize can be serious

• Commonly missed syndromes: occult pulmonary embolism in medically healthy young women, complex partial seizures due to early head trauma (sports concussion?) or more serious neuropathology

• Pheochromocytoma ("cold fear") or hyperthyroidism (easy to test for) are rare
EFFECTS OF MEDICAL ILLNESS ON ANXIETY TREATMENT OUTCOME IN THE CALM STUDY

ANXIETY AND WRONG PRIMARY DIAGNOSIS

• Somatic Symptom Disorder—Somatic symptoms a core part of anxiety
• Atypical Bipolar Disorder with alternating mixed anxious states and more dysphoric depressions
• ADHD—most often confused with GAD
• Occult Substance Abuse—much more common than you think, especially in middle and upper income patients
Somatic Symptom Disorder

• Formerly Somatization Disorder-low rate
• Somatic symptoms causing distress/dysfunction
• Cognitions, or anxiety, or behavior change focused on “seriousness” of symptoms
• Not explained by another disorder
• The key differentiating factor is often the persistence of thoughts, feelings or behaviors, persistent help seeking despite normal tests, antagonism to psychological explanations
• Relation to anxiety probably dimensional
Somatic Symptom Presentations
Common to all Mood and Anxiety Disorders

Fig. 1. Prevalence of clusters of somatic symptoms across controls and patients with a depressive and/or anxiety disorder.
Differential Diagnosis

- Panic more episodic but not when chronic!
- Depression has depressive symptoms
- GAD has multiple worries not just one
- Conversion has loss of neurologic function and so an “objective” finding
- Delusional disorder—beliefs are more firmly held and sometimes bizarre
- BDD—concern is appearance
- OCD—symptoms more intrusive
Somatic Symptom Disorder

• In general, pharmacotherapy is not very effective. There are no RCTs but even observational series are underwhelming—I would use SSRIs along with an atypical antipsychotic

• CBT has been more effective—Cochrane review (2014) of 21 studies indicates ES of 0.34 (small to moderate) for all therapies but CBT studies the most rigorous and numerous (n=14)
CBT for Somatic Symptom Disorder

Fig. 2 Change in the primary outcome measure – the Health

Hedman et al The British Journal of Psychiatry 2016 Aug 6 online
doi: 10.1192/bjp.bp.116.181396
## CBT for Somatic Symptom Disorder

<table>
<thead>
<tr>
<th>Health Anxiety Inventory (scale range: 0–192)</th>
<th>Mean (s.d.)</th>
<th>Effect size (95% CI)</th>
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<tbody>
<tr>
<td></td>
<td>Pre-treatment</td>
<td>Post-treatment</td>
</tr>
<tr>
<td>ICBT</td>
<td>105.5 (21.4)</td>
<td>69.7 (24.8)</td>
</tr>
<tr>
<td>U-ICBT</td>
<td>109.1 (25.8)</td>
<td>68.8 (33.6)</td>
</tr>
<tr>
<td>Bibliotherapy</td>
<td>114.5 (21.3)</td>
<td>75.5 (35.0)</td>
</tr>
<tr>
<td>Control condition</td>
<td>108.2 (24.1)</td>
<td>100.1 (26.1)</td>
</tr>
</tbody>
</table>


a: Between-group effect sizes are based on the control condition as comparator.
ELEVATED RATES OF ANXIETY DISORDER IN BP ILLNESS
CAN ANXIETY BE A DISGUISED “MIXED” BP STATE?

• In comorbid anxiety and BP, anxiety precedes BP diagnosis by 3 years
• Anxiety predicts transition from MDD to BP illness in adults
• Anxious children of BP parents have high rate of agitation/irritability with antidepressants
• Mixed states often misdiagnosed as anxiety
• What does preference for BZs mean in these cases?
Mixed features of depression: why DSM-5 is wrong (and so was DSM-IV)

Athanasios Koukopoulos, Gabriele Sani and S. Nassir Ghaemi

The DSM system has never acknowledged a central position for mixed states; thus, mixed depressions have been almost completely neglected for decades. Now, DSM-5 is proposing diagnostic criteria for depression with mixed features that will lead to more misdiagnosis and inadequate treatment of this syndrome. Different criteria, based on empirically stronger evidence than exists for the DSM-5 criteria, should be adopted.

TREATMENT APPROACHES

• Combination Treatment

• RCTs in Treatment Resistance

• Novel Approaches
COMBINATION TREATMENT

- Most studies done in non-refractory anxiety
- Slight advantage of combination treatment in panic disorder
- Equivocal evidence of combination treatment advantage in GAD
- Consistent evidence of combination treatment advantage in SAD
- Combination treatment not better than ERP in OCD
- No data in PTSD—ongoing UW study
CAN BZS ADVERSELY IMPACT THE EFFICACY OF PSYCHOTHERAPY?

• Old literature suggests BZs may impair desensitization to specific phobias
• Uncontrolled studies suggest BZ use is associated with increased anxiety sensitivity since patients improve with BZ cessation (Fava et al 1994)
• Westra et al (2002) show prn BZ users have poorer CBT outcome than non-users or regular users
• As needed (prn) use of BZs is often employed in addition to regular dosing by users
• PRN use reduces self-efficacy (reinforces pill taking as a coping mechanism) and interferes with stress tolerance by linking anxiety contexts with BZ intake and promoting conditioned tolerance (Westra and Steward 2002)
GAD With Depressive Symptoms: Could BZs Make Anxiety Worse?

* Imipramine/diazepam > placebo $P < 0.05$.
** Imipramine > diazepam $P < 0.05$.
BZD = benzodiazepine.

Eszopiclone Added to an SSRI Improves Anxiety Outcomes in GAD

NNT for:
Response=6
Remission=15

RCTS IN TREATMENT RESISTANT ANXIETY
Adjunctive Paroxetine in Panic Disorder Non-Responders to CBT

Kampman et al 2002

N=38
All p<.05
IN CBT REFRACTORY PANIC, WOULD MORE CBT WORK AS WELL AS PAROXETINE?

<table>
<thead>
<tr>
<th>Assessment</th>
<th>SSRI n (%)</th>
<th>Continued CBT n (%)</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time 3 (3 months)</td>
<td>18/31 (58%)</td>
<td>8/21 (38%)</td>
<td>2.25</td>
<td>.72 – 6.99</td>
</tr>
<tr>
<td>Time 4 (12 months)</td>
<td>13/23 (57%)</td>
<td>8/15 (53%)</td>
<td>1.24</td>
<td>.41 – 3.70</td>
</tr>
</tbody>
</table>

Response to treatment in assessed participants.
RESPONSE RATES FOR CBT VS TAU IN MEDICATION RESISTANT ANXIETY: THE CALM STUDY (N=258)

NNT=5

Roy-Byrne et al unpublished; from Roy-Byrne et al 2010 JAMA
TREATMENT-REFRACTORY ANXIETY: AUGMENTATION RCTS

- BZ to SSRI for SAD
- Pregabalin to SSRI for SAD
- Risperidone augmentation for GAD (but largest trial negative in PTSD)
- Olanzapine augmentation for GAD and PTSD
- Open trials for anticonvulsant augmentation (Gabapentin, Tiagabine, Leviracetam for all four disorders); buspirone augmentation (SAD); antidepressant combinations (Panic)
SSRI-REFRACTORY SAD: BZ ADVANTAGE?

Remission CZ, VEN, SERT = 27%, 19%, 17% NS
Response CZ, VEN, SERT = 56%, 46%, 36% CZ > SERT

Pollack et al, 2014
ADJUNCTIVE PREGABALIN FOR SSRI REFRACTORY SAD

Rickels et al 2012

mean change in HAM-A total score. On the basis of repeated measures analysis of covariance using the heterogeneous autoregressive variance structure with treatment, center, week, and treatment-by-week as fixed effects and baseline HAM-A total score as a continuous covariate. M-A, Hamilton Anxiety Rating Scale; LS, least squares.
ATYPICAL NEUROLEPTICS; HIGH RISK, LIMITED GAIN?

- **Strongest data** support adjunctive use, added to SSRI, in OCD (Olanzapine, Risperidone, Quetiapine, Aripiprazole)—but inferior to add on ERP!
- Remaining data possibly supports adjunctive use (olanzapine and risperidone) **only in some** cases of PTSD (but recent large negative risperidone study).
- No studies in panic, no efficacy in GAD, unclear in SAD
- Adverse effects on lipids, glucose and weight much better established than clinical benefits!
- Thus, Quetiapine monotherapy results were NOT sufficient to get FDA approval for GAD
- **Adjunctive use** is third line option in disabling, resistant anxiety—**Bzs are probably much safer overall, and with better evidence for efficacy!**
ATYPICAL NEUROLEPTICS NOT EFFECTIVE IN REFRACTORY GAD

LaLonde et al 2011 J Clin Psychopharmacol
ERP BEATS RISPERIDONE IN REFRACTORY OCD

Simpson et al 2013, JAMA Psychiatry
Adjunctive Risperidone Treatment for Antidepressant-Resistant Symptoms of Chronic Military Service–Related PTSD

NOVEL MEDICATION APPROACHES: RCTS

• Anticonvulsants
  -- Gabapentin (panic, SAD); Pregabalin (GAD, SAD)
  -- Valproate (panic, but 2 negative trials in PTSD)
  -- Tiagabine (GAD, but follow up trial negative)
  -- Lamotrigine (PTSD, but very small study)

• Atypical Neuroleptics
  --- Quetiapine (Robust data in GAD)
  --- Olanzapine (SAD, but negative trial in PTSD)

• Prazosin (PTSD nightmares)

• Inositol (2 studies in panic)

• Open trials support ACs in panic, SAD, PTSD, and atypicals in PTSD—But don’t believe open trials!
NOVEL NON-MEDICATION APPROACHES: RCTS

• Exercise (in panic, but may apply to others)
• Imagery Rehearsal (PTSD, but could apply to GAD and other ruminative syndromes)
• Mindfulness?
LIMITED BENEFIT OF EXERCISE FOR ANXIETY?

**TRIAL**
- Herring-Wait-List 2011
- Broocks – Placebo 1998
- Herring - Resistance Training 2011
- Wedekind 2010
- Wedekind (SSRI) 2010
- Martinsen 1989

**Wait-List/Placebo Comparison**
- Herring-Wait-List 2011
- Wedekind 2010
- Wedekind (SSRI) 2010
- Martinsen 1989

**Non-Aerobic Exercise Comparison**
- Merom 2008
- Jazaieri 2012

**Other**

**TOTAL**

**Fig. 3.** Measured effect size of aerobic exercise for anxiety disorder stratified by the type of comparison condition.
EXERCISE, CLOMIPRAMINE, AND PLACEBO FOR PANIC

- Aerobic Exercise (n=11)
- Clomipramine (n=15)
- Placebo (n=11)

*Brooks et al., 1998*
Imagery Rehearsal vs. Wait List for Nightmares in PTSD

Krakow et al 2001
## MBSR FOR GAD

<table>
<thead>
<tr>
<th>Measure &amp; Condition</th>
<th>Pre-Treatment M (SD)</th>
<th>Post-Treatment M (SD)</th>
<th>3-month FU M (SD)</th>
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<tbody>
<tr>
<td><strong>Primary Outcomes</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Clinician’s Severity Rating</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>MBSR</td>
<td>6.02 (1.09)</td>
<td>3.09 (2.59)</td>
<td>2.18 (2.66)</td>
</tr>
<tr>
<td>CBT</td>
<td>6.08 (.86)</td>
<td>3.22 (2.81)</td>
<td>2.94 (2.83)</td>
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<tr>
<td>Penn State Worry Questionnaire</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>MBSR</td>
<td>45.46 (9.83)*</td>
<td>39.37 (13.59)</td>
<td>44.73 (13.02)</td>
</tr>
<tr>
<td>CBT</td>
<td>39.75 (12.32)*</td>
<td>39.75 (12.59)</td>
<td>40.00 (11.58)</td>
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<td>MASQ-Anxious Arousal Scale</td>
<td></td>
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<tr>
<td>MBSR</td>
<td>21.05 (8.64)</td>
<td>20.30 (8.41)</td>
<td>17.69 (7.15)</td>
</tr>
<tr>
<td>CBT</td>
<td>20.23 (8.60)</td>
<td>17.14 (8.02)</td>
<td>16.85 (8.53)</td>
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<td><strong>Secondary Outcomes</strong></td>
<td></td>
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<tr>
<td>Beck Depression Inventory-II</td>
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<tr>
<td>MBSR</td>
<td>25.97 (11.61)</td>
<td>21.36 (15.26)</td>
<td>24.53 (15.68)</td>
</tr>
<tr>
<td>CBT</td>
<td>22.12 (12.32)</td>
<td>19.10 (14.81)</td>
<td>20.42 (16.55)</td>
</tr>
</tbody>
</table>

Arch et al 2013 Beh Res Therapy
"I was able to get in one last lecture about diet and exercise."
TREATMENT RESISTANCE: ASSESSMENT APPROACH

• Is it treatment resistance—rating scale data!
• Is it pseudo-resistance—are you delivering correct type, “dose” (therapy elements) for long enough? Is the patient adherent?
• If true treatment resistance, assess: health habits, wrong diagnosis, medical comorbidity
TREATMENT RESISTANCE: PHARMACOLOGIC APPROACHES

- Start with antidepressant baseline (SSRI vs venlafaxine?)
- Wait long enough (?) for complete response
- Adjunctive treatments—consider another AD, BZD, atypical antipsychotic, anticonvulsant, pindolol?
- Other possibilities—NAC, SAMe, Deplin?
- Simplify regimen after 6–12 months
TREATMENT RESISTANCE: PSYCHOTHERAPY APPROACHES

• CBT useful alone or in combination with medication for
  – Refractory symptoms
  – Persistent cognitive factors, behavioral patterns and anxiety sensitivity
  – Comorbid conditions
  – Early intervention for PTSD prophylaxis

• CBT may be facilitated by medication if it did not work alone

• Some anxious patients may need an alternate approach

• Psychodynamic psychotherapy, IPT, Mindfulness could be tried
"Why should I settle for good self-esteem when, with the right medication, I could have great self-esteem?"