TREATMENT-RESISTANT DEPRESSION

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Question 1

Common reasons for antidepressant treatment failure include:

A. Inadequate antidepressant dose or duration

B. Poor compliance with treatment regimen

C. Behavioral factors such as active stressors or personality disorder

D. Incomplete or erroneous diagnosis

E. All of the above

Question 2

Which of the following is a standard approach to treating resistant depression?

A. Optimization of current antidepressant treatment

B. Dose increase

C. Switch to alternate antidepressant

D. Augmentation or co-prescribing approach

E. All of the above

Question 3

Which of the following antidepressant switches is not considered helpful in treatment resistant unipolar depression?

A. SSRI to SSRI

B. SSRI to SNRI

C. SSRI to lithium

D. TCA to SNRI

E. SSRI to bupropion

Question 4

Which of the following augmenters has not been shown effective in treating resistant depression in randomized controlled trials?

A. Modafinil

B. Pindolol

C. Buspirone

D. All

E. None

Question 5

Which coprescribing approach is supported by randomized controlled trials in treatment resistant depressive patients?

A. SSRI + mirtazapine

B. TCA + SNRI

C. SSRI + SSRI

D. All

E. None

Antidepressant Efficacy: Limitations of Current Agents

- 29% to 46% of depressed patients show partial or no response to initial antidepressant trial[1]
- Many “responders” live with
  - Partial improvement
  - Adverse effects
- Residual symptoms are associated with greater relapse/recurrence risk[1]

1. Fava and Davidson. Psych Clin No Am 1996;19:179-200.

Treatment Resistance: Thase and Rush Staging Method

- Stage I: Failure of at least one adequate trial of one major class of antidepressant
- Stage II: Stage I resistance plus failure of adequate trial of an antidepressant in a distinctly different class from that used in Stage I
- Stage III: Stage II resistance plus failure of an adequate trial of a TCA
- Stage IV: Stage III resistance plus failure of an adequate trial of a MAOI
- Stage V: Stage IV resistance plus failure of a course of bilateral ECT

from Petersen et al. J Clin Psychopharmacol 2005;25:336-41

Treatment Resistant: Newer/Broader Conceptions

- MGH Staging Method assigns points for each failed intervention and predicts remission more successfully than Thase/Rush approach[1]
- Given high rate of partial responders, “treatment resistance” concept is sometimes applied to patients with residual symptoms regardless of resistance staging.

1. Petersen et al. J Clin Psychopharmacol 2005;25:336-41.

What Constitutes an AdequateTherapeutic Trial?

Treatment resistance or inadequate treatment?

- Appropriate antidepressant choice?
- Adequate dose?
- Adequate duration?
- Plasma levels (TCAs only)?
- Treatment adherence assured?

"ABCD" Evaluation Approach to Antidepressant Treatment Resistance

- **A**dequacy of prior treatment
  - Duration of treatment
  - Dosage of medication
- **B**ehavioral/Environmental factors
  - Personality disorder
  - Psychosocial stressors
- **C**ompliance/Adherence
  - Patient education
  - Treatment intolerance
- **D**iagnosis
  - Missed medical diagnosis
  - Missed psychiatric diagnosis

Adequacy of Treatment

- Many depressed patients receive inadequate treatment
  - In one study, only 23% of trials used adequate doses
  - Nearly half improved once given adequate doses
- Duration too brief is another source of failure
  - In one study, 25% of previous nonresponders to various antidepressants responded when trial was extended from 4 to 6 weeks (vs. 8% of placebo subjects)

Behavioral Factors

- Family conflicts
- Poor family support
- Marital partner perceived as uncaring
- Multiple losses, bereavement
- Job-related stress
- Financial stress

Compliance (Adherence)

- Perhaps accounts for 20% of treatment resistance
- Contributors to noncompliance (nonadherence):
  - Distress is denied or externalized
  - Effect of medication is inadequate, side effect intolerable
  - Access to treatment is obstructed
  - Relationship with prescriber is obstructive
- Potential consequences of nonadherence:
  - Suboptimal response
  - Relapse or recurrence
  - Discontinuation symptoms

Diagnostic Challenges:

1. Specific Depressive Subtypes may suggest specific treatment modifications

A. Depression with anxiety

B. Depression with psychotic features

C. Atypical depression

D. Depression with substance abuse

E. Bipolar depression

F. Depression with personality disorder

A. Depression with Anxiety Disorder – Treat Anxiety Disorder Too

- PTSD
- Social Anxiety/Social phobia
- Agorophobia
- Panic disorder/panic attacks/limited Sx attacks
- GAD
- OCD

Lydiard & Bawman-Mintzer, 1999

B. Depression with Psychotic Features

- Delusions or hallucinations
- Typically mood-congruent
- Associated with:
  - Increased severity
  - More frequent hospitalization
  - More frequent suicide
  - Less frequent spontaneous remission
- Combination pharmacotherapy needed

C. Depression With Atypical Features

- Mood reactivity
- At least two of:
  - Significant weight/appetite increase
  - Hypersomnia
  - Leaden paralysis
  - Longstanding rejection sensitivity resulting in significant social/occupational impairment
- Not melancholic or catatonic
- Present during most recent 2 weeks of depressive episode or predominant during most recent 2 years of dysthymic disorder

D. Depression With Substance Abuse

- Depression can worsen Substance Abuse
- Substance abuse can worsen Depression
- Antidepressants can help one or both disorders
- Abstinence is an important step in diagnosis
- Comorbid or alternate diagnoses may be present
- Hospitalization may be required

E. Depression in Bipolar Disorder

- Major Depressive Episode may herald Bipolar Disorder
- Antidepressant monotherapy may trigger hypomanic/manic response
- Antidepressant monotherapy may destabilize course of Bipolar Disorder
- Anticonvulsant therapy is not an optimal treatment for unipolar depression

F. Depression With Personality Disorder

- Predisposition, complication, or independent comorbid disorder?
- Poorer antidepressant response
- Treatment complicated by
  - Dysfunctional attitudes
  - Maladaptive attributional style
- Role of psychotherapy

Diagnostic Challenges:

2. Concurrent medical illness may require specific disease-targeted treatment

- Endocrine disorders
- Metabolic disturbances
- Collagen-vascular diseases
- Infectious disorders
- Neoplastic disorders
- Neurologic disorders
- Toxic disorders

Diagnostic Challenges:

3. Concurrent Medications or Recreational Substances may cause or contribute to depressive symptoms

- Antihypertensives
- Steroids
- Sedative-hypnotics
- Hormonal treatments
- Alcohol
- Sedatives
- Stimulants (withdrawal phase)

Diagnostic Challenges:
4. Cognitive Impairment

- Neurodegenerative disorders may produce prodromal depressive symptoms but may require specific treatment instead or or in addition to antidepressant
- Cognitive impairment may represent “Dementia Syndrome of Depression”
- Biological and psychodiagnostic testing may help to differentiate

Pharmacotherapy of Treatment Resistant Depression: Next Step

- Optimize
- High Dose Therapy
- Switch
- Augment/Co-prescribe
- ECT
- Psychotherapy

First Optimize Current RX

- Dose
- Duration of Treatment
- Drug Levels Where Appropriate
- Antidepressant Choice in Subtypes
  - Comorbid anxiety: SSRI, MAOI
  - Psychotic features: antipsychotic
  - Atypical depression: Consider MAOI, ?SRI
  - Bipolar depression: Begin with mood stabilizer

Optimization of Current Rx

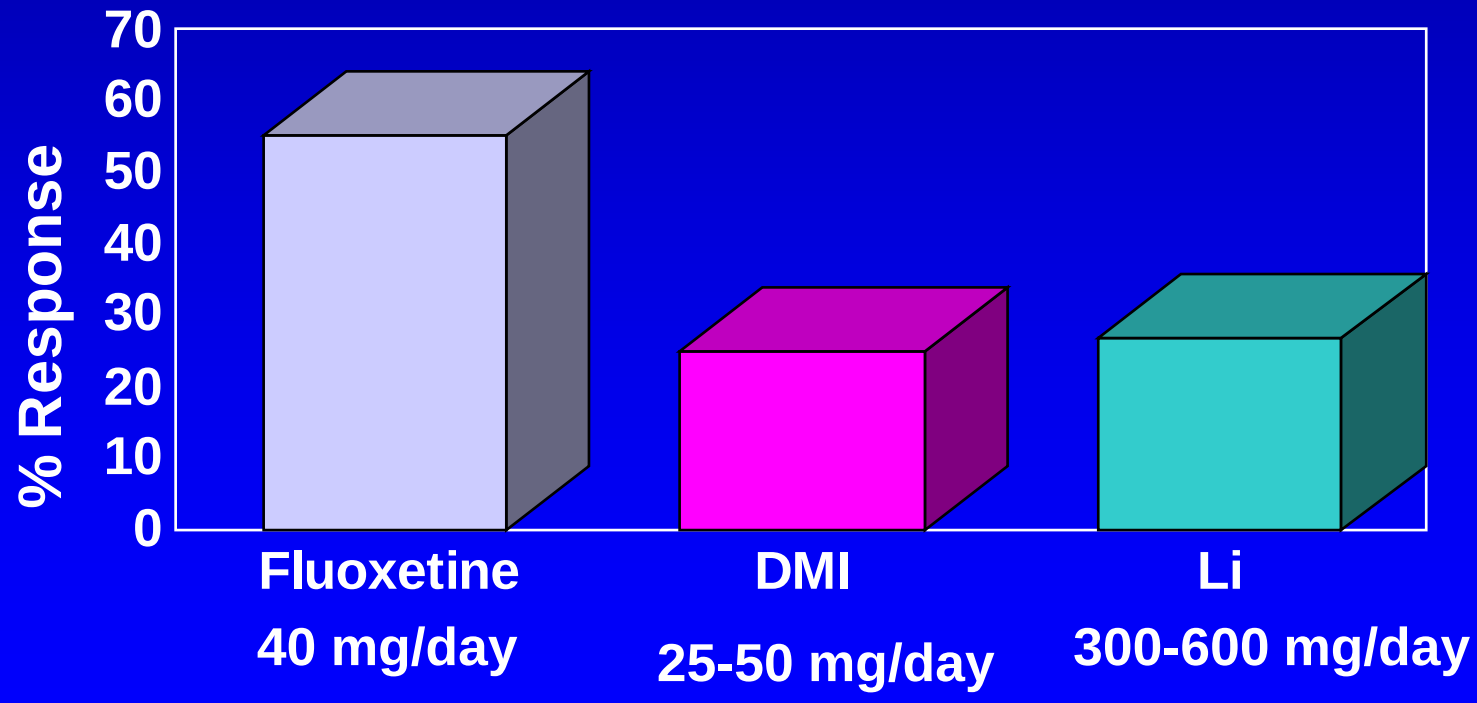
- Simple and essential
- Verify adherence and proper use of medication
- Listen carefully to side effect concerns and address them to extent possible
- Ask specifically about:
  - Weight concerns
  - Sexual side effects
  - Sleep disturbances

Rationale for Higher Dose Treatment with Initial Agent

- Easy and may buy time that will facilitate response
- Drug concentration at the “site of action” (the brain) affected by
  - Differences in drug bioavailability (e.g. brand vs generic)
  - Inter-patient pharmacokinetic variability
  - Percent protein bound (% free to cross BBB)
- Steady-state levels at same mg/kg dose vary up to 1000%; 300-500% common

Dose Increase vs Augmentation or Combination

After failed 8 week trial of fluoxetine 20 mg/day, 41 subjects randomized to 5 weeks of 40 mg/d vs fluoxetine 20 mg/d with either DMI or Li



Fava et al., 1994

Very High Dose Antidepressant Therapy

- Tricyclic plasma levels may be low at maximal recommended oral doses
- High dose MAOI therapy anecdotally reported
- Support for high dose SSRI treatment is limited

Potential “Switches” After SSRI Failure[1]

- SSRI to SSRI: Several open-label studies demonstrate that as many as 50% of nonresponders to 1 SSRI may respond to another. No SSRI is “first choice” for switch.
- SSRI to TCA: Two double-blind studies demonstrate high response rates with switch of nonresponders from paroxetine or sertraline to imipramine but side effect rate is high.
- SSRI or TCA to SNRI: Several studies support switch to SSRI and one double-blind trial showed switch from TCA or SSRI to venlafaxine 200-300 mg/d was more likely to achieve response (52%) or remission (42%) than was paroxetine (33% response, 20% remission).

1. Nelson JC. J Clin Psych 2003;64[suppl 1]:5-12

Potential “Switches” After SSRI Failure[1]

- SSRI to bupropion: Small trial showed response in 28% of nonresponders switched from fluoxetine 40 mg or greater.
- SSRI to mirtazapine: Mixed findings
- Switch to MAOI: Mixed findings

1. Nelson JC. J Clin Psych 2003;64[suppl 1]:5-12

Antidepressant “Augmenters”

- Augmenters with established effectiveness:
  - Lithium carbonate
  - Triiodothyronine
- Co-prescribing strategies:
  - SSRI + TCA
  - Antidepressant + Bupropion
  - Antidepressant + Mirtazapine
- With possible effectiveness
  - Stimulants
  - Dopaminergic agonists
  - Pindolol
  - Buspirone
  - Atypical antipsychotic
- Other proposed augmentations strategies
  - Modafinil
  - Estrogen
  - Testosterone
  - Lamotrigine
  - Folate
  - Dexamethasone
  - Ketoconazole
  - Inositol

Lithium Augmentation

- Studied withTCAs, MAOIs, SSRIs
- Begin with 300 mg hs and increase weekly by 300 mg hs.
- Response does not require high level
- Potential concerns:
  - Complexity of regimen and monitoring
    - Blood levels
    - Thyroid and renal monitoring
  - Patient acceptance/side effects/toxicity

Thyroid Hormone Augmentation

- Rationale is enhancement of norepinephrine receptor sensitivity
- Dose: 25-75 mcg/d of T3 (T4 less studied)
- Side effects may occur
- Studied primarily with TCAs (only case report data with SSRI augmentation)
- Measure TSH before initiating treatment to:
  - R/o thyroid disease as contributor to symptoms
  - Establish baseline for monitoring
  - Attempt to shift TSH to lower quartile of reference range and not into hyperthyroid range

SSRI + TCA (1)

- Preliminary findings suggested this combination for accelerating response[1,2]
- Open trials showed 65% response rate[2,3,4]
- Increased TCA plasma levels suggested to contribute to higher response rate[5,6]
- Two randomized trials found this combination less effective than “dose increase” of initial antidepressant.

1. Baron et al. 1988; 2. Nelson et al. 1991; 3. Weilburg et al. 1991;
4. Nelson et al. 1991. 5. Bergstrom et al. 1992; 6. Levitt et al. 1999

SSRI + HCA: Potential Risks

- Side effects (e.g. in Fava et al. 2002):
  - Dry mouth 55.9%
  - GI distress 47.1%
  - Dizziness 35.3%
  - Insomnia 32.4%
  - Agitation 29.4%
  - Sedation/Fatigue 26.5%
- Serotonin syndrome
- Anticholinergic toxicity
- Cardiotoxic HCA levels

SSRI or SNRI + Bupropion[1-4]

- Based on 1 review and 3 open trials – but no double-blind RCT
- Subjects included partial responders and non-responders. There were inadequate controls on subjects' prior response to one of the combined ADs
- Bodkin et al series[1]:
  - Majority of subjects on benzodiazepine or mood regulator
  - SSRI (fluoxetine) doses[1]: 20-60 mg/d, Bupropion doses[1] 100-450 mg/d
- Tripling of venlafaxine blood level (though not SSRI level) with addition of bupropion[4] in one study may partially explain response

1. Bodkin et al. 1997; 2. Marshall and Liebowitz 1996; 3. Spier 1998; 4. Kennedy et al. 2002

Possible Differential Effects of Co-Prescribing Bupropion vs SRI[1]

- 70% showed improvement with either approach
  - Adding **bupropion**
    - Energy, motivation improved in many
    - Sexual function improved in some
    - Sleep worsened in some
  - Adding **SRI**
    - anxiety improved, energy worsened
- Adverse effects similar to monotherapy

1. Bodkin JA et al. J Clin Psych 1997;58:137-45.

SSRI + Bupropion: Potential Risks

- Excessive stimulation
- Tremor
- Panic attacks
- Increased risk of seizures
- Toxic elevated OH-bupropion levels
- Discontinuation from AE in one study = 15%[1]

1. Bodkin JA et al. J Clin Psych 1997;58:137-45.

SSRI or NDRI + Mirtazapine(1)[1]

- Following preliminary positive results[1], RCT evaluated antidepressant augmentation of SSRI (83%) or bupropion or venlafaxine with mirtazapine (15 mg/d x 7 d, then 30 mg/d) in 26 outpatient depressed non- or partial-responders[2]
- Mean pre-combination treatment 19.4 wks

1. Carpenter et al. 1999; 2. Carpenter et al. 2002.

SSRI or NDRI + Mirtazapine(2)[1]

- Response rates: Mir 63.6% vs Pla 20%
- Remission rates: Mir 45.5% vs Pla 13.3%
- Discontinuation for AE similar to placebo
- Most frequent side effect = weight gain
- Concerns:
  - No data on effect of mirtazapine alone
  - Switch from ineffective SSRI in another study showed 37.8% remission with mirtazapine[2]

1. Carpenter LL, Yasmin S, Price LH. Biol Psych 2002;51:183-8;
2. Thase, Kremer, Rodreques: IPS poster 2000

SSRI or NDRI + MIR: Potential Risks

- Anticholinergic toxicity (HCA or paroxetine)
- Serotonin syndrome (clomipramine)
- Sedation
- Weight gain
- Elevated mirtazapine levels from 2D6 inhibition

Other AD Combinations[1]

MAOI + TCA*	Limited response rate; high AE rate; In the only RCT, ECT was superior
RIMA + SSRI or TCA	High rate of side effects limits response
NaSSA (Mianserin) + TCA*	Response enhanced; AE not increased
NaSSA (Mianserin) + SSRI*	Response enhanced and accelerated
NaSSA (MIR) + SNRI (VEN)**	No dedicated study found
NaSSA (MIR) + BUP**	No dedicated study found
SNRI (VEN) + BUP	Bup increases Ven levels[3]; anxiety
SNRI (VEN) + SSRI	Antichol effects[2]; Serotonin syndrome
SNRI (VEN) + TCA	+ findings in preliminary case series
SSRI + SANPA (NEF)	mCPP with 2D6 inhibiting SSRIs
SSRI + Reboxetine	May have different SE than SSRI+Ven
SSRI + SSRI	Two open studies[1] (CIT+FLV;Various)

**RCT available. **No study published. 1. Lam et al. J Clin Psychiatry 2002;63:685-93. 2. J Clin Psych 2002;63:181-6. 3. Young SJ. J Clin Psych 1996;57:177-8.*

Stimulant Augmentation of SSRIs

- Choice of agent:
  - Methylphenidate (10 - 40 mg/d)
  - Dextroamphetamine (5 - 20 mg/d)
- Extolled for rapid effect, popular in medical settings
- Used with
  - TCA, MAOI, SRI (no evidence base for use with SRI)
- No controlled studies
- Effect may be transient
- May increase TCA levels, exacerbate insomnia or anxiety or anorexia, can increase HR and BP
- Abuse potential in patients with history of SA

Dopaminergic Agonist Augmentation of SSRIs

- Choice of agent:
  - Pergolide and bromocriptine, used in past, may be less safe than current selective agonists
  - Pramipexole and Ropinirole are currently used, though with limited open-label support
- May also improve sexual dysfunction
- May exacerbate anxiety/psychosis?
- Associated with potentially dangerous somnolence
- Limited data support -- more studies are needed

Pergolide Augmentation of Antidepressant

Dose = 1–5 mg

- Pergolide
  - potent D_1, D_2, and D_3 agonist
  - duration of action: 24 hours
  - used for Parkinson's
  - Significant potential adverse effects
- Antidepressant effects
  - does not work alone
  - 55% significantly better
  - better mood, interest, energy often seen

Bromocriptine Augmentation Of Antidepressants

Six-Week, Uncontrolled, Open Study (N=6)

- Dosing
  - initiate at 7.5 mg qd
  - titrate up to 52.5 mg qd if needed
- Response
  - 67% with ≥50% improvement
  - Responders better in ≤2 weeks

Inoue et al., Biol Psych 1996

Pramipexole Augmentation

- 23 subjects with TRD were followed after a 16 week open label trial of pramipexole augmentation of TCA or SSRI treatment
- 12 were treated for resistant major depression, 11 for resistant bipolar depression
- Dose range: 0.375 – 1.5 mg/d; Mean dose 0.990 mg/d
- Median time to sustained remission = 10 weeks
- 60.9% of subjects responded
- 35.7% of remitters experienced recurrence between 24 and 28 weeks
- Side effects:
  - No sleep attacks
  - 2 cases of hypomania
  - 1 case of psychotic mania

Cassano P et al. Depress Anxiety 2004;20:131-8

Ropinirole Augmentation

- 16 week open-label pilot study assessed ropinirole in TRD
- N= 10 (7 unipolar, 3 bipolar II)
- 0.25 to 1.5 mg daily added to TCA or SSRI
- Mean maximum dose was 1.33 mg/d
- 4 of 10 (40%) patients were responders
- Dizziness led to 2 discontinuations

Cassano P et al: Can J Psychiatry 2005;50:357-60

Pindolol Augmentation of SSRIs

- Mechanisms
  - decreases beta-adrenergic activity
  - antagonizes $5HT_{1A}$ autoreceptor but not postsynaptic receptor, thus increases postsynaptic serotonin release
- Typical dose 2.5 mg tid
- Appears to accelerate response to SSRI in double-blind trials
- Not proven to increase response among treatment resistant depressives

Nelson C. J Clin Psychiatry 2003;64[suppl 1]:5-12

Buspirone Augmentation of SSRIs

- Rationale: $5HT_{1A}$ partial agonist
- 20-50 mg/d
- Low in side effects and reported (inconsistently) to counteract SSRI-associated sexual dysfunction
- 5 open series reported successful augmentation of SSRIs in TRD but 1 double-blind controlled study (with very high placebo rate) did not confirm this and a second controlled study showed initial greater improvement vs placebo that was lost by 6 weeks except in the most severe third of the subjects.

Nelson C. J Clin Psychiatry 2003;64[suppl 1]:5-12

Atypical Antipsychotic Augmentation (1)

- Lower EPS than typicals, but associated with other significant adverse effects (e.g. metabolic, vascular)
- Proposed mechanism:
  - Antagonism of $5HT_2$ receptors (all atypicals)
  - Antagonism of $5HT_{1a}$ receptors (ziprasidone, aripiprazole)
  - Antagonism of $5HT_{1d}$ autoreceptors (ziprasidone, risperidone)
  - D_2 agonist activity (aripiprazole)
  - Reuptake inhibition for NE, 5HT, DA (ziprasidone)
  - Increased prefrontal levels of DA and NE (olanzapine)

Nelson C. J Clin Psychiatry 2003;64[suppl 1]:5-12

Atypical Antipsychotic Augmentation (2)

- Risperidone: Several positive open-label studies support use with SSRI, typical dose 0.5 to 1 mg/d
- Olanzapine: Several small studies and 1 double-blind trial (dose 5-20 mg/d with fluoxetine) support augmentation of SSRI
- Ziprasidone+SSRI: 20-80 mg bid, open label
- Aripiprazole+SSRI or SNRI: 2.5-5 mg/d, open label
- Only anecdotal support for antidepressant augmentation with quetiapine, clozapine

Papakostas GI. Essential Psychopharm 2005;6:209-220;
Nemeroff CB. J Clin Psychiatry 2005;66[suppl8]:13-21

Modafinil Augmentation

- Open label study assessed doses of 100-400 mg/d in 21 patients with hypersomnia and partial antidepressant response
- 43% of subjects showed significant response (score reduction of >50% on the Major Depression Inventory)
- Inconsistent findings in other open label trials has led to limited support of this costly polypharmacy, though it is easily implemented and may be appropriate in some hypersomnic patients

Rasmussen NA et al. Nord J Psychiatry. 2005;59:173-8

Estrogen Augmentation

- Limited support for this historical approach
- Most often tried in post- and peri-menopausal women
- Limited use related to concern about risk of breast cancer and endometrial cancer
- Further safety concerns raised by WHI findings
- Gradually increase from 1.25 mg to 3.75–4.375 mg qd X21 days
- Intermittent use of progesterone 5 mg qd for 5 days permits menstruation

Testosterone Gel Augmentation

- 8 week randomized, placebo-controlled trial with 23 men aged 30-65 with “refractory depression” and low or borderline testosterone
- 22 randomly assigned to 10 g of 1% testosterone gel q d vs placebo in addition to ongoing antidepressant
- Serum total testosterone levels were 350 ng/dl or less
- Beware increased risk of prostate cancer, screen for elevated PSA prior to treatment
- Improvement in affective and vegetative symptoms seen

Pope HG Jr et al. Am J Psychiatry 2003;160:105-11

Lamotrigine Augmentation

- Various anticonvulsants have been used as antidepressant augmenters, with minimal empirical support.
- Lamotrigine, shown to be antidepressant in bipolar patients, has some support for use in unipolar treatment resistant depression from a chart review of 37 indivduals
  - 6 discontinued because of adverse events
  - 31 on lamotrigine for at least 6 weeks took mean dose of 112.90 mg/d
- Response rates:
  - 40.5% very much or much improved
  - 21.6% mildly improved
  - 37.8% unchanged
- Trend toward increased response with comorbid anxiety and/or chronic pain syndromes

Barbee JG, Jamhour NJ: J Clin Psychiatry. 2002 Aug;63(8):737-41

Folate

- Rationale: Low plasma and RBC folate measurements have been linked to poor antidepressant response
- In this double-blind controlled study, 127 depressed (not treatment resistant) subjects on fluoxetine 20 mg/d received folic acid (500 mcg/d) or placebo
- Folate increased (less in men than in women) and homocysteine levels decreased in women
- Better antidepressant response in the women was associated with folate augmentation
- Need for higher folate dose in men was hypothesized

Coppen A, Bailey J. J Affect Disord. 2000 Nov;60(2):121-30.

Dexamethasone Augmentation

- N=10 TRD subjects (failed 6 weeks on fluoxetine or sertraline) in open label trial
- Dexamethasone 3 mg/d x 4 days was added to ongoing antidepressant
- Dexamethasone treatment was associated with significant improvement in 6 subjects and minimal response in 2
- Good clinical response associated with high baseline cortisol level

Dinan TG et al. Acta Psychiatr Scand. 1997;95:58-61

Ketoconazole Augmentation

- 11 studies have addressed antiglucocorticoid treatment of major depression
- Response rates reach 67-77%
- Studies' sample sizes are small and mostly open-label

Wolkowitz OM and Reus VI. Psychosom Med. 1999;61:698-711

Inositol Augmentation

- Rationale: Deficiency in inositol (precursor or postsynaptic second messenger)
- Early anecdotal reports supported efficacy of 6 g inositol/day in reducing the severity of depressive conditions
- A double-blind placebo-controlled study of SSRI plus 12 g/day inositol did not improve “refractory depression”

Nemets B et al. J Neural Transm 1999;106:795-8

Psychotherapy for TRD

- Several controlled and uncontrolled trials support the value of psychotherapy in treatment resistant depression
- Cognitive behavioral and psychoeducational approaches have been the most studied and supported
- Need for more high-quality studies of other therapy approaches

McPherson S et al. Acta Psychiatrica Scandinavica 2005;111:331-340

ECT

- After several failed pharmacotherapy trials, ECT is recommended by some authorities when:
  - Patient accepts
  - “Modified” ECT is available and not medically contraindicated
- Unilateral first may be preferred
- Rapid relapse or history of relapses on medications suggests use of maintenance ECT

Refractory to ECT?

- Try bilateral treatments
- Verify adequate (>30 sec) seizure duration
  - discontinue sedative/hypnotics that may interfere with seizures
  - Consider augmenting seizure with:
    - theophylline 200 mg on night before
    - hyperventilation X2–3 minutes
    - caffeine 250–500 mg IV (decreases seizure threshold but not duration)

Vaagal Stimulation for Refractory Depression

- 29 depressed patients failing at least two full AD trials at adequate doses
- Vagal implant into neck vs sham
- 30 sec pulse with 3-4 min rest
- 30% recovered (some after acute trial with continued rx-as low as HAMD of 5)
- Appears to be sustained
- Some pain, vocal difficulty, reversible

AJ Rush et al, 1999

Conclusions

- Limited evidence supports several approaches to treating resistant depression with optimization, switch, or augmenting/co-prescribing approaches
- Controlled data are lacking for many treatment strategies in common use
- More hypothesis-testing studies are needed, with consistent definitions of treatment resistance
- Best sequence for interventions is not yet established

Question 1

Common reasons for antidepressant treatment failure include:

A. Inadequate antidepressant dose or duration

B. Poor compliance with treatment regimen

C. Behavioral factors such as active stressors or personality disorder

D. Incomplete or erroneous diagnosis

E. All of the above

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