TREATMENT-RESISTANT DEPRESSION

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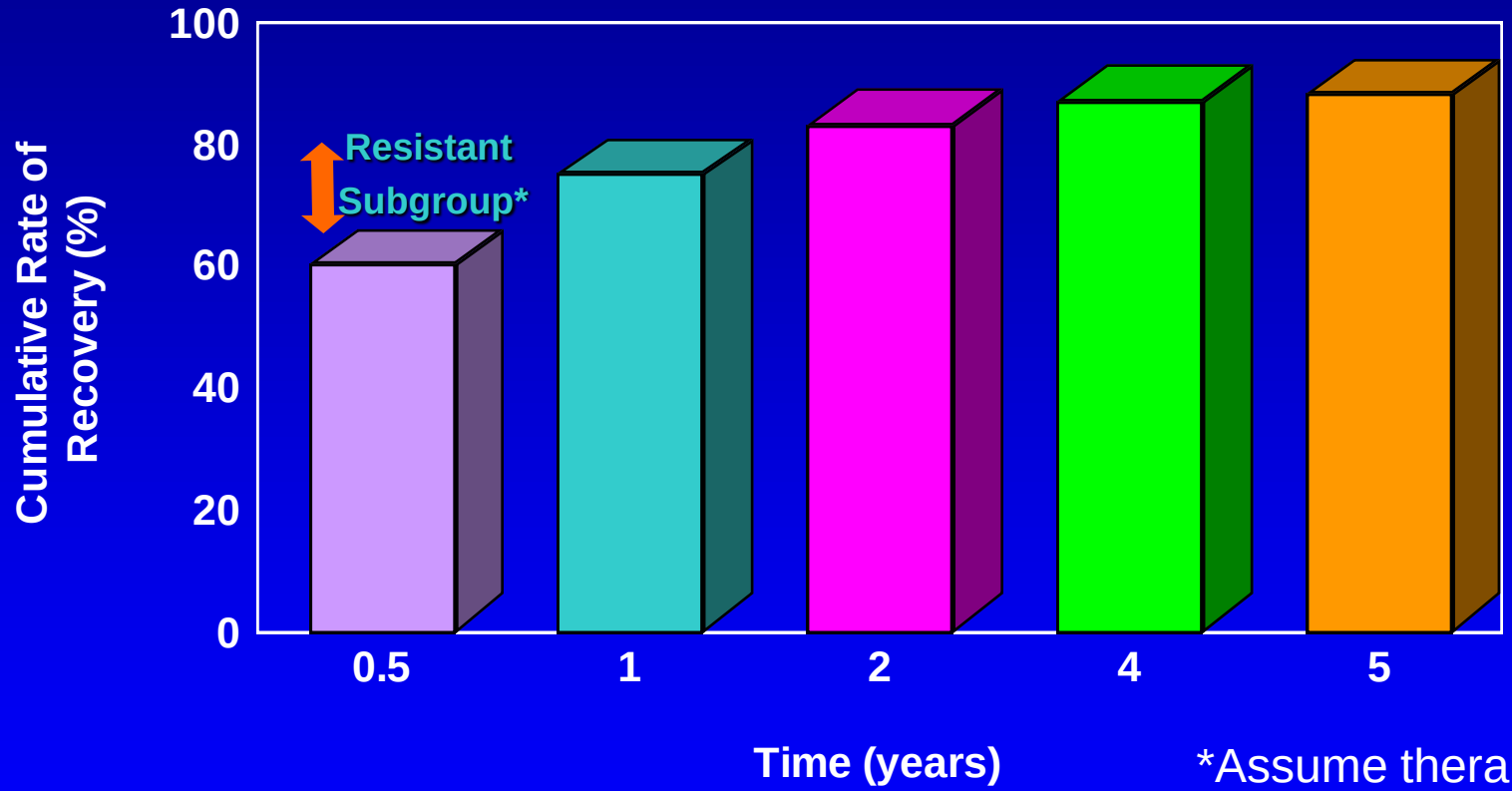
Naturalistic Recovery Rates of MDE Over 5 Years



*Assume therapeutic trial completed

From Keller, 1994

Definitions

- Therapeutic Trial
- Treatment “resistant” vs “refractory”
- Stages of Treatment Failure
- Augmentation
- Combination treatments

Therapeutic Trial: Two or more documented failures

Was it treatment resistance or inadequate treatment?

- Adequate dose for 4-6 weeks?
- Plasma levels (TCAs only)?
- Compliance otherwise documented?
- Diagnosis need revision?
- Best antidepressant for mood subtype?
- Main initial task is detective work

Definition of Treatment Resistance

- Major depression, correctly diagnosed
- Failure to respond to 1 or 2 adequate trial(s) of antidepressant treatment
- Different from partial response
- Different from recurrence or relapse

Treatment Resistance: Suggested "Stages"

I. Failure of at least one adequate trial
II. Failure with two classes of AD
III. TCA nonresponse + ≥1 other classes
IV. Stage III plus MAOI nonresponse
V. Stage IV plus ECT nonresponse

Rush and Thase, 1994

Eventual Outcome in Resistant Depression

- 40–50% - Remission
- 10–15% -Unimproved
- 20–30% - Relapse or recurrence first
- Residual symptoms are common

REFRACTORY DEPRESSION

Traditional term for failure to respond to the first agent use

Evaluation of Antidepressant Treatment Resistance

- Adequacy of prior treatment
  - Duration of treatment
  - Dosage of medication
- Behavioral/Environmental factors
  - Personality disorder
  - Psychosocial stressors
- Compliance
  - Patient education
  - Treatment intolerance
- Diagnosis
  - 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. Cognitive Impairment

- Cognitive impairment may represent depressive “pseudodementia”
- Dementing disorders may produce depressive symptoms
- Biological and psychodiagnostic testing may help to differentiate
- Antidepressant treatment may be helpful adjunct in treating dementia

Diagnostic Challenges:

2. Concurrent Medical Illness

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

Diagnostic Challenges:

3. Concurrent Medications or Recreational Substances

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

Diagnostic Challenges:

4. Complex Depressive Subtypes

A. Depression with psychotic features

B. Atypical depression

C. Depression with substance abuse

D. Bipolar depression

E. Depression with personality disorder

A. 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

B. 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

C. 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

D. 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

E. Depression With Personality Disorder

- Predisposition, complication, or coaggregation?
- Poorer antidepressant response
- Dysfunctional attitudes
- Maladaptive attributional style
  - personal responsibility, magnitude, permanence
- Role of psychotherapy

Check for Comorbid Anxiety: 60 % of Patients have at least one Anxiety Disorder

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

Lydiard & Bawman-Mintzer, 1999

Pharmacotherapy of Treatment Resistant Depression: First Optimize -- then Increase, Switch or Augment?

- Increases may succeed, may buy time
- Class switches succeed 50% of time
- Switches may be simpler
- Augmentation may be faster
- Choice is based on:
  - Tolerability and effectiveness of initial drug
  - Patient preference, time pressure
  - Ability to comply

Obvious Reasons for AD Treatment Failure

- Oral dose prescribed (MD) or taken (patient)
- Inadequate duration of treatment
- Biological differences in non-bipolar depression subtypes (atypical, melancholia)
- Breadth of efficacy for comorbid disorders
- Side effects burden
- Psychoeducation/ collaborative contract
- Psychosocial and environmental variables

Less Obvious Reasons for Failure to Respond to Treatment

- Drug concentration at the “site of action” (the brain) affected by
  - Differences in bioavailability in marketed drugs
  - Inter-patient pharmacokinetic variability
  - Percent protein bound (% free to cross BBB)
  - Compliance
- Steady-state levels at same mg/kg dose range up to 1000%; 300-500% common

First Optimize Current RX

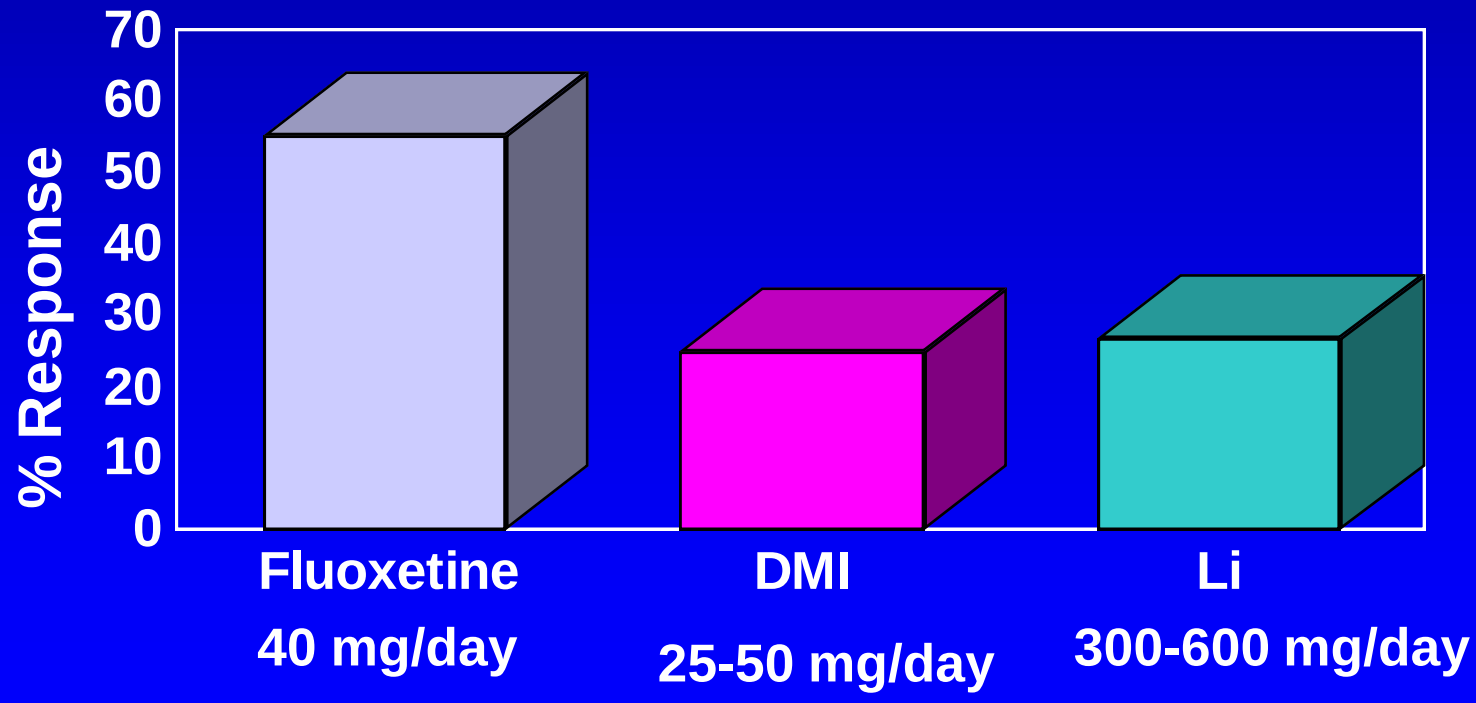
- Dose
- Duration of Treatment
- Drug Levels Where Appropriate
- Antidepressant Choice in Subtypes
  - Comorbid anxiety: SSRI, MAOI
  - Atypical: MAOI, ?SSRI

Optimization of Current Rx

- Counteract unwanted effect
- Propranolol for tremor
- Bethanechol for dry mouth, urinary retention
- Antiparkinson agent for EPS
- Zopiclone or zolpidem for insomnia
- Bupropion for sexual side effects

OPTIMIZATION vs AUGMENTATION/COMBINATION

Failed Fluoxetine 20 mg/day for 8 Weeks
N=41
Randomized to 5 Weeks



Fava et al., 1994

High Dose Antidepressant Therapy

- Tricyclic plasma levels may be low at maximal recommended oral doses
- High dose MAOI therapy anecdotally reported
- Mixed opinions about high dose SSRI treatment

Antidepressant “Augmenters”

- An additional antidepressant
  - *Bupropion, Tricyclic, SRI, Mirtazapine, MAOI
- +Lithium carbonate
- +Thyroid hormone
- + Stimulants
- + Dopaminergic agents
- + Buspirone

Miscellaneous Augmenters

- Atypical antipsychotic
  - Risperidone (0.5 - 2 mg/d)
  - Olanzapine (5 - 20 mg/d)
- Estrogen
- Antiepileptic drug
- Dexamethasone (3 mg/d x 4 days)
- SAM-E
- Ketoconazole
- Inositol
- Reserpine
- Verapamil

Adjunctive Atypical Neuroleptics

- Risperidone, clozapine, olanzapine
- Direct antidepressant effects
- Best data in severe bipolar depression

Lithium Augmentation of Desipramine & Fluoxetine

- 30 patients in each group
- All failed adequate trial
- 60% responded in each group
- Fluoxetine patients responded faster
- 33% of the fluoxetine group relapsed; 0% of the desipramine group relapsed

ONTIVEROS & FONTAINE

Antidepressant Augmentation

Moderate Levels of Li Are Better

	Response(%)
• Placebo	4/18 (22%)
• 250 mg Li (0.2)	6/34 (18%)
• 750 mg Li (0.7)	15/34 (44%)
	p<0.001

Response within 6 weeks ususal

Stein & Bernadt, 1994

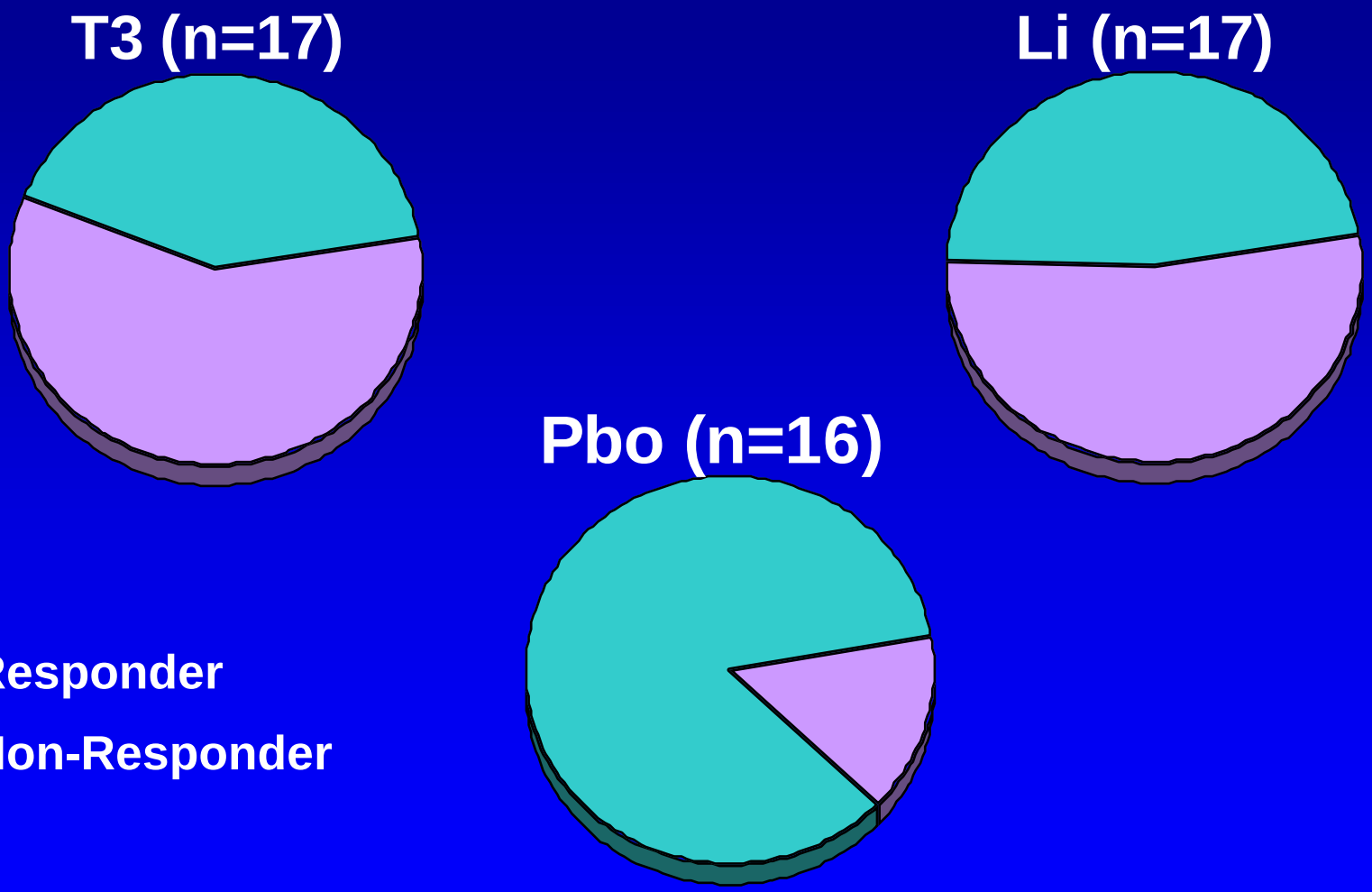
RESISTANT DEPRESSION
Lithium vs T_3 Augmentation

- N=50: TCA-resistant patients (>2.5 mg/kg X5 weeks)
- Random Assignment: 2 weeks

			Response
Li+	**(17)**	**900-1200 mg/day**	**10/17**
T3	**(17)**	**37.5 mcg/day**	**9/17**
Pbo	**(16)**		**3/16**

Joffe et al., AGP 1993;50:387

LITHIUM vs T_3 AUGMENTATION



Joffe, 1993

T_3 AUGMENTATION

- Combined studies
  - 50 µg: 55% response
    - may help females > males
  - 25 µg: placebo response
- Always get TSH first to rule out hyperthyroidism

Thyroid Augmentation of TCAs May Be Helpful

Euthyroid Depressed Patients

		Response
• T_3	37.5 µg	9/17 (53%)
• T_4	150.0 µg	4/21 (19%)*

*Significantly worse than placebo response

Some evidence for combined T3,T4 as useful (Prange et al, 1999) in pts on replacenent thyroid with this combo

Joffe et al., 1991

T_3 ABNORMALITY

- Sick euthyroid syndrome
  - starvation or illness
  - often decreased T_4 to T_3 conversion
  - may see increased inactive rT_3 with decreased T_3
- Low T_3 most often seen in older females, particularly with bipolar I or II disorder

WHEN TO USE T_4 vs T_3

- T_3 (50 mg)
  - euthyroid treatment-resistant depression
  - sick euthyroid syndrome
    - beware T_3 • ¬TSH • ¬T_4 • ¬T_3
- T_4
  - depressed, hypothyroid
    - may need to try out various “euthyroid” levels
  - rapid cycling bipolar women

Augmentation with Benzodiazepines

- Recent controlled data suggest short-term clonzepam useful for early augment agent and for chronic MDE
  - Smith et al, AJP 1998; 155:1339-45
  - Morishita et al JAD 1999 53: 275-8
- Benzodiazepines for Initial Anxiolytic/ Sedative Effects

SSRI +`Buspirone Augmentation

- 3 open trials (n=36, 3 wks Rx, 20–50 mg)
  - 75% response rate
- 1 double-blind, placebo-controlled trial (n=117, 4 wks Rx)
  - buspirone (n=54)
    - 60% improved
    - 52% “very much or much improved”
  - buspirone vs placebo
    - no statistical difference secondary to high placebo rate

Bakish, 1991; Jacobsen, 1991; Joffe & Schuller, 1993; Fahlen T, unpublished

Sleep Deprivation Augmentation If On Lithium Or Antidepressant

- 30% improvement in 1 day, sustained 2–5 days later
  - not sustained if not on Li or antidepressant
- If sustained response seen, sleep deprivation can be repeated q4–7d to increase response
- Effective in about 50–55% of patients
- If sleep deprivation is successful, may need maintenance sleep deprivation

TIMING of SLEEP DEPRIVATION AUGMENTATION for LITHIUM or ANTIDEPRESSANT

- May be result of REM deprivation
- If one night deprivation (patient only sleeps 4 hours)
  - 1st half deprivation: ineffective*
  - 2nd half deprivation: effective

*1 study reported effective

Stimulants And Dopaminergic Agents Are Used As Adjuncts

- Dopaminergic hypothesis of depression
- Methylphenidate
- Dexedrine
- Bromocriptine
- Amantadine
- (Pergolide)
- Pramipexole

Stimulants for Depression

Primary care (9/10)	placebo = stimulant
Geriatric (4/5)	methylphenidate > placebo
Medically ill	methylphenidate or dextroamphetamine > placebo
Treatment-resistant	methylphenidate or dextroamphetamine > placebo
Side effects	insomnia, tremors, anorexia, tachycardia, blood pressure (up or down)

Stimulant Augmentation

- QD dosing
  - methylphenidate 10–40 mg
  - D-amphetamine 5–30 mg
  - Pemoline 18.75–75 mg/day
  - Amantadine 100-200mg/day
  - Advantages
  - tolerance (adverse effects uncommon)
  - decreases hypotension
  - Rx comorbid ADD, sleep apnea
- Disadvantages
  - increases TCA levels
  - can worsen insomnia, anorexia
  - can increase HR, increase or decrease BP

Psychostimulants in Refractory Depression

Guidelines and Recommendations

Should Be Considered After
Standard Therapies Fail

- Chronic, treatment-resistant unipolar depression/dysthymia
- Medically ill, depressed geriatric patients
- ADHD with chronic depression
- Hypersomnia with chronic depression

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
- Antidepressant effects
  - does not work alone
  - 55% significantly better
  - better mood, interest, energy often seen

Pergolide Was Found to Help When Added to a Variety Of Antidepressants

- Agonist D_1, D_2, D_3, and $\__2$-adrenergic
- N=20 (unipolar = 16, bipolar = 4)
- Added to DMI, NT, Dox, Fluox, Fluox+Amox, TRZ, Alpraz, and nothing
- Dose starting 0.05 to 0.25 mg
- Increases 0.1 mg q3days
- Target dose 2 mg

Boukoms & Mangini, 1993

Pergolide Was Found To Help When Added To A Variety Of Antidepressants

- Much or very much improved 11
  Minimally improved 3
  No improvement 3
  Worse 3
- ADRs included nausea and anxiety
- Efficacy within 1–4 weeks
- Follow-up until 35 weeks

Boukoms & Mangini, 1993

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 ε50% improvement
  - _ responders better in ≤2 weeks

Inoue et al., Biol Psych 1996

Pindolol Is Among The Newer Augmentations For Increasing Speed Of Response

Pindolol 2.5 mg TID

- Mechanisms
  - decreased beta-adrenergic activity
  - antagonizes 5HT1A autoreceptor but not postsynaptic receptor, thus increases postsynaptic serotonin release
- 4 open-label studies on variety of ADs
  - TCA, SSRI, trazodone, MAOI, nefazodone
  - majority responded within 1 week

Artigas & Blier, 1995; Maes, 1996; Bikish, 1997

Pindolol Is Among The Newer Augmentations For Increasing Speed Of Response

Pindolol 2.5 mg TID
3 Double-Blind, Placebo-Controlled Trials

- 1 study with fluoxetine = no efficacy (Berman, 1997)
- 2 studies with paroxetine
  - significantly accelerated response by day 4 (Tome, 1997; Thomas, unpublished)
  - best responders
    - ≤2 prior treated episodes of depression
    - moderate or lower depression severity

Ketoconazole

- Cortisol biosynthesis inhibitor
- Outcome
  - hypercortisolemic group (4 p.m. cortisol ε11): 48% decrease in HAM-D
  - normal cortisol group = placebo
- Monitor for Na (¬), K ( ), cortisol (lab norm)

Reus V et al. Bio Psych New Research Abstracts, 1996

Estrogen Augmentation

- Most often tried in post- and peri-menopausal women
- Risk of breast cancer and endometrial cancer
- Gradually increase from 1.25 mg to 3.75–4.375 mg qd X21 days
- Then progesterone 5 mg qd for 5 days to permit menstruation

Estrogen Augmentation

- Take prenatal vitamins also (extra B_6, etc.)
- Estradiol may have more brain effect than conjugated estrogens
- Case reports suggest some men benefit from testosterone

Tachyphylaxis

- Too high level
  - nortriptyline, fluoxetine?
- Too low level
  - may see intermittent responsiveness
- Tolerance
  - time off drug (3 month to 2 years) and then return to it
- Consider augmentations

Lithium Does Not Speed Imipramine Response

- N=22
  - imipramine + lithium (n=11)
  - imipramine (n=11)
- Imipramine dose = 150–175 mg
- Lithium dose = 600–1200 mg
- Antidepressant effect
  - imipramine + lithium no faster or greater overall benefit than imipramine alone

Buspirone Augmentation Of Antidepressants

- Bakish, 1991
  - Buspirone augmentation in fluoxetine non-responders (n=3)
- Jacobsen, 1991
  - Buspirone effectiveness in 7 of 8 antidepressant (7 SSRI) non-responders
  - Enhances response in 8 of 9 winter relapsers (5 SSRI)
- Joffe & Schuller, 1993
  - 7 of 25 respond to buspirone augmentation (12/16 fluoxetine, 5/9 fluvoxamine)

Change/Switch ADs

From	To	Response
TCA	TCA	30%
TCA	SSRI	60%
TCA	MAOI	60%
SSRI	SSRI	60%
SSRI	TCA	60%
SSRI	MAOI	60%
MAOI	MAOI	30%
MAOI	TCA	60%
MAOI	SSRI	60%

Based on experience of authors

Changing Classes of ADs

- Discontinuation effects
  - Pharmacodynamic effects of prior treatment
  - May potentiate/hasten new treatment effects
  - May change likelihood of A/Es
- Concern over clinical effects on mood
  - Suggest adding second agent, then tapering first
- Few empirical data

SSRI Non-Response Does Not Predict Another SSRI Non-response in Outpatients

Outpatients

- First SSRI — no response
- Second SSRI — 51% good response
- In very treatment-resistant inpatients and outpatients, there is <30% chance of response to another SSRI

SSRI Intolerance Does Not Predict Another SSRI Intolerance In Outpatients

Outpatients
4-Week Washout Between Treatments, n=112

Couldn't Tolerate	New Intolerance Rate
Sertraline	Fluoxetine 1%
Fluoxetine	Sertraline 10%

Brown. J Clin Psych 1995

Dropouts Secondary To Side Effectsa

Paroxetine	21%
Venlafaxine	19%
Mirtazapine	16%
Nefazodone	16%
Sertraline	15%
Fluoxetine	15%
Bupropion SR	9%
TCAs	30%
Tertiary	>32%
Secondary	26%

Low Suicide Risk

- Fluoxetine
- Sertraline
- Paroxetine
- Bupropion
- Trazodone
- Venlafaxine
- Nefazodone
- Citalopram
- Mirtazapine

Treatment-Resistant Depression

Bupropion

- TCA nonresponders (n=1,301)
  - 54% had good or better response to bupropion
- Fluoxetine nonresponders
  - 47% responded to bupropion
- Bupropion's unique mechanism of action may be an advantage

Predictors Of Tricyclic Response

- Increased response
  - insomnia
  - anorexia
  - psychomotor retardation
  - anhedonia
  - insidious onset
  - guilt
- Decreased response (response to TCA ≤50% with only 1 of the following symptoms
  - hypersomnia*
  - hyperphagia*
  - mood worse in p.m.*
  - panic/severe anxiety (TCAs initially worsen this)

*Atypical symptoms

Blood Levels and Clinical Response

Drug	Curvilinearity*	Optimal Plasma Levels (ng/ml)
Nortriptyline	+	50–150
Amitriptyline	+?	70–180 total
Imipramine	–	225 total
Protriptyline	+?	70–150
Doxepin	+ (?)	100–200
Desipramine	+ (?)	100–200

For imipramine, doxepin, desipramine, & amitriptyline: typical dose to give effective plasma dose is 3 mg/kg

* + curvilinearity = “therapeutic” with too low or high dose less effective

Age and Confusional Risk with TCAs

Age	Risk Rate
10–29	0%
30–39	4%
40–49	25%
50–59	33%
60–69	43%
70–79	50%

Serotonin Reuptake Inhibitors vs TCA

- Typical depression: same
  - TCA possibly superior in geriatric/severe melancholic depression (controversial)
- SSRI superior in depression with
  - panic disorder,hypersomnia,hyperphagia,mood reactivitymood. worse in p.m., profound anergy
  - delusions (?) “n”
  - Premenopausal and estrogen-supplmented women may respond better to SSRI; Postmenopausal women respond better to TCAs
    - Limited data

Beware of "False Intolerance" Related to Medication Switch

TCA to SSRI

- Example
  - desipramine 200 mg failed
  - desipramine decreased to 150 mg
  - start fluoxetine or paroxetine
- Result
  - patient complains of anxiety, sweating, tachycardia
  - patient never takes SSRI again

Differential Effects of ADs

- Atypical depression-MAOIs and SSRIs>TCAs
- Agents with 5-HT reuptake inhibition more broadly effective than TCAs, bupropion

Chronic Depression
Mean Duration 18 Years

80% Atypicals (n=153)

	Responders
Phenelzine	70%
Imipramine	46%
Placebo	17%

Venlafaxine for Refractory Depression

- 70 unipolar
- Mean HDRS
- Documented failure of at least:
  - 3 adequate antidepressant trials
  - 1 attempt at augmentation
- Rapid titration up to 376 mg
- 32.9% responded acutely

Nierenberg et al., 1994

Nefazodone in Resistant Melancholia

- HAM-D average: 29.7
- Average dose: 500 mg
- Nefazodone response: 54%
- Placebo response: 18%
- Percent of treatment-resistant patients was not reported

MAOI Responder Profile

- Typical depression
  - Post (1980) studies suggest efficacy = TCA
- Depression with panic disorder
- Atypical depression
  - hypersomnia
  - hyperphagia
  - mood worse in p.m.
  - (increased reactivity ?)
- Refractory depression
  - regular dose
  - high-dose Parnate (90–170 mg)

High-dose Tranylcypromine In Resistant Depression

Descriptive Features of the Patients

Pt #	Present Episode (yr)	# Previous Treatments	# Previous Combinations	# ECT	Max Dose (mg)
1	8	14	2	14	120
2	8	13	5	28	170
3	8	7	1	12	100
4	19	3	0	0	130
5	2.5	7	1	0	120
6	25	8	1	0	170
7	9	9	1	0	90
8	8	6	0	0	120
9	1.5	7	0	0	120
10	20	22	5	37	110
11	1.5	2	0	0	180
12	14	15	4	0	120
13	2	5	1	0	120
14	2	8	0	0	120

Amsterdam, 1995

Refractory to ECT

- Unilateral • bilateral
- Short (<30 sec) seizures
  - discontinue meds (sedative/hypnotics)
  - theophylline 200 mg on night before
  - hyperventilation X2–3 minutes
  - caffeine 250–500 mg IV decreases seizure threshold but not duration (neurotoxic in rats given ECT)
- Relapsing?
  - lithium

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

ACE Inhibitors

- Angiotensin Converting Enzyme (ACE) inhibitor
- ACE in hippocampus, amygdala, hypothalamus, cortex
- Degrades neuropeptides including CRF
- May reduce HPA axis activity and cortisol production

Captopril in TRD

- Double-blind, controlled trial
  - captopril 150 mg/day (n=8)
  - placebo (n=6)
- Captopril group had greater reduction in HDRS ($p<0.06$) and CGI rating ($p=0.05$)

Germain & Chouinard, 1988

Buprenorphine For Refractory Depression (n=10)

- Buprenorphine: μ-opiate receptor partial agonist
- Solution dose (a.m.): 0.15 mg begin
  1.26 mg average
  1.8 mg maximum
- Route: intranasal or sublingual
- HAM-D: pre 28.1
  week 1 17.6
  final (4–6 weeks) 10.7
- 50% dropouts secondary to side effects (nausea, sedation)

Bodkin et al. J Clin Psychopharm 1995;15(1)

Antidepressant Effect Of Nicotine Patch In Nonsmokers (Never)

- N=12, major depression with HAM-D > 18
- Patch
  - each 17.5 mg X24 hours (Nicotinell®)
- Design
  - 4 days on patch, 4 days off
  - not on antidepressant

Antidepressant Effect Of Nicotine Patch In Nonsmokers (Never)

	Hamilton Depression 21 Item*	Hamilton 10 Item*
Pre	28.8	17
4 days on patch	12.5	2.5
Post 4 days off	27	16.5

*p<0.001

Salin-Pascall. J Clin Psych 1996

Treatment-Resistant Depression

Subtype of Depression

- Choose medication most suitable for:
  - typical depression
  - atypical depression
  - dysthymic disorder
  - psychotic depression
  - bipolar depression

DYSTHYMIC DISORDER

Most with "Typical" Symptoms

4 Weeks Rx	Imipramine = Placebo = 50%
6 Weeks Rx	Imipramine (74%) > Placebo (50%)
Conclusion	High placebo response Need longer trials

- Dysthmia responds to SSRIs well

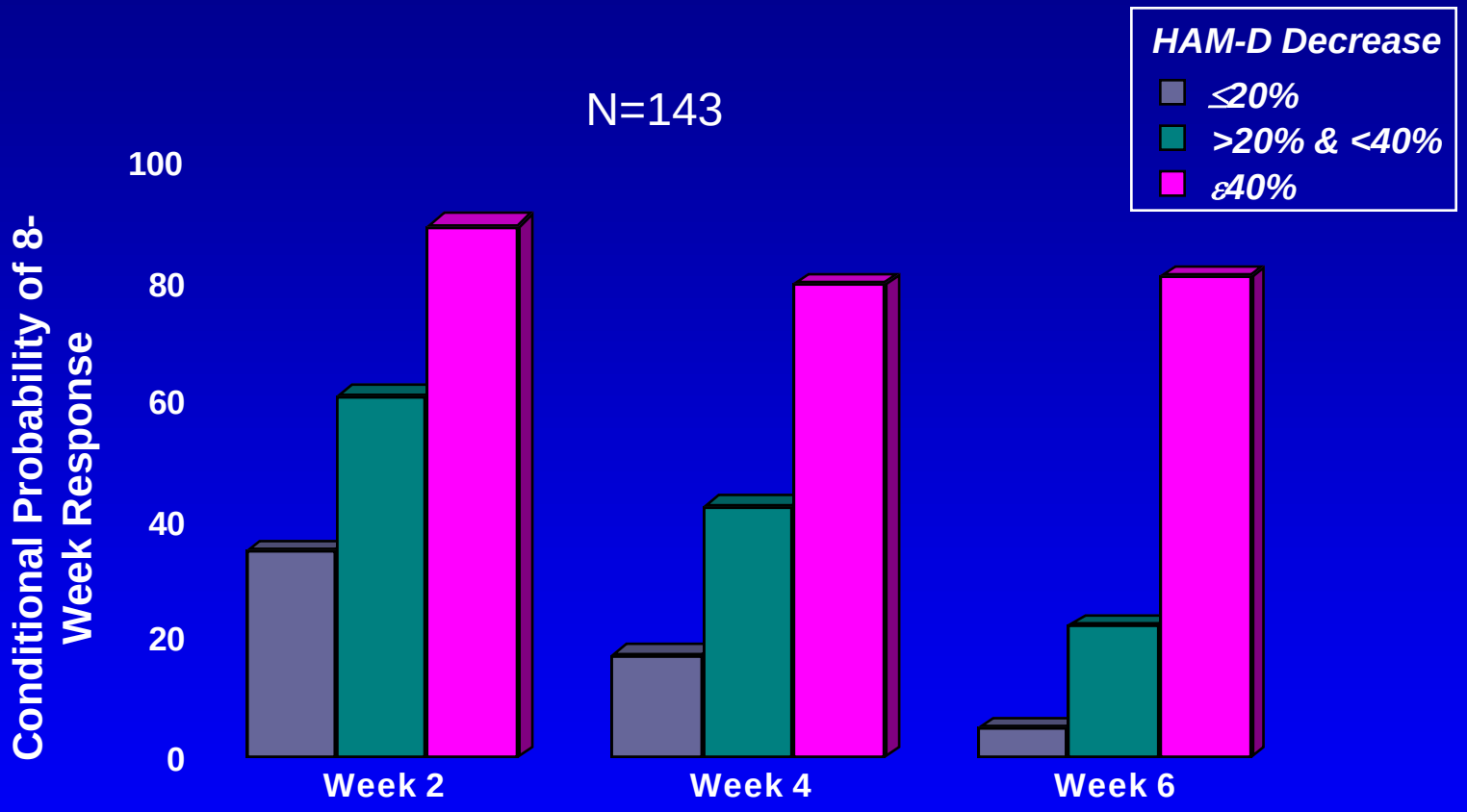
Adjunctive Neuroleptics

- First choice for psychotic depression
- Probable choice for
  - “soft” psychotic symptoms
  - negative over-valued ideas
  - disorganized thinking
- Avoid low-potency neuroleptics

Minimal Antidepressant Response

- 3–5 weeks of treatment
- Consider
  - increased dose, if well-tolerated
  - augmentation with another drug

Early Non-response To Fluoxetine Predicts 8-week Outcome (>50% Decrease in HAM-D)



Suggests by week 4 if #20% response a change in treatment approach is indicated (dosage, augmentation, or different drug)

Nierenberg et al., 1995

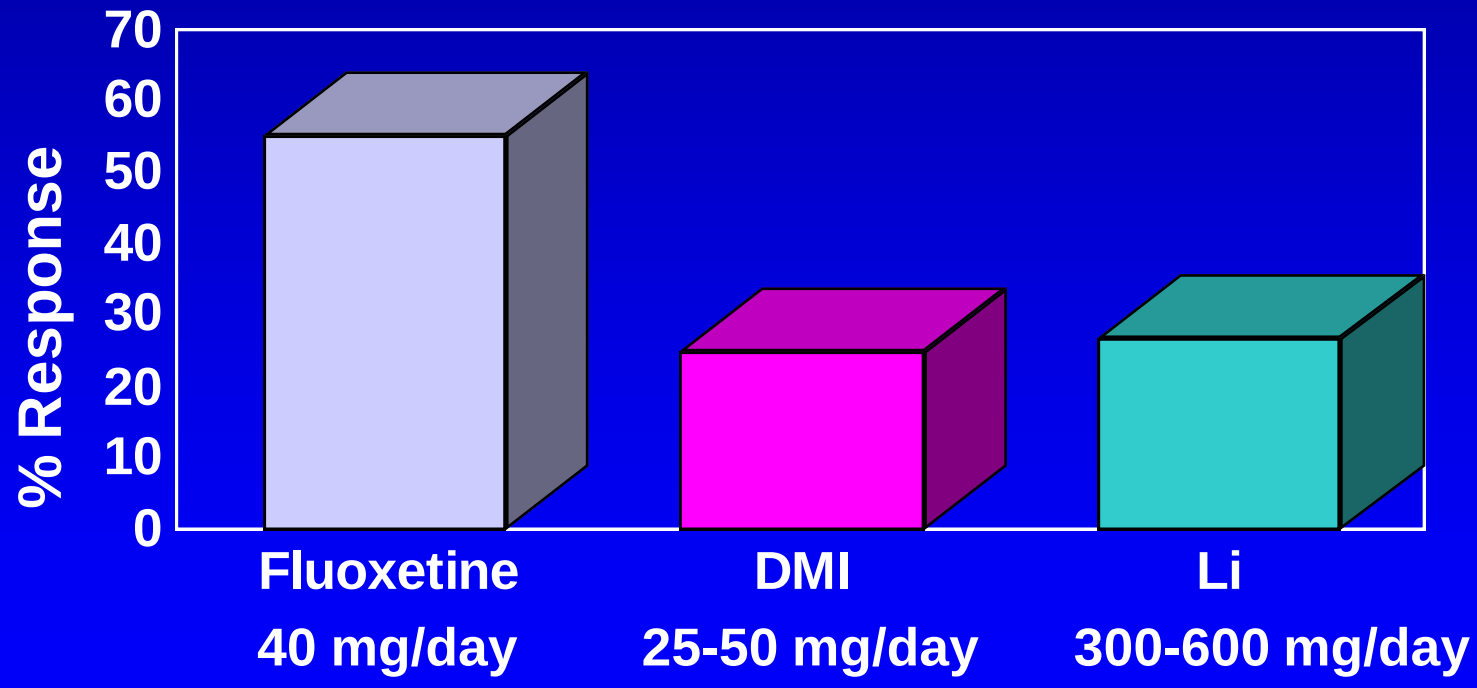
Increase Drug Dose, ADD Lithium Augmentation or ADD TCA To Failed Trial Of Fluoxetine

- Increased dose 8/15 (53%)
- Li augmentation 4/14 (29%)
- Add DMI 3/12 (25%)
  p=0.24
- Caveat emptor
  - low doses of Li (600 mg) and DMI (50 mg), but with fluoxetine level averages ♠3X higher

Fava et al., 1994

Optimization vs Augmentation/Combination

Failed Fluoxetine 20 mg/day for 8 Weeks
N=41
Randomized to 5 Weeks



Fava et al., 1994

Fluoxetine-Resistant Depression

- 8 week trial
  - 20 mg
- Increase dose to 40–60 mg X4 weeks
  - partial responders 83% improved
  - nonresponders 33% improved
- Add augmentation
  - nonresponders 50% improved on Li
  - partial responder 40%

Fava et al., 1994

Fluoxetine-Resistant Depression Conclusions

- If partial response, increase dose
- If no or minimal response
  - try augmentation
  - consider another antidepressant

Women And Stimulants

Frequent Dysphoric Response In:

- Postmenopausal women
- Atypical depression
- Borderline personality disorder

Treatment Documentation

- Documenting treatment and outcome can avoid replicating efforts in future
- Rating scales
- Specifics of dose, duration, plasma levels

Conclusions

- Controlled data lacking
- Hypothesis-testing studies needed
- Combination treatment often works better
- Duration of combined or augmentation not cleat
- Welcome to psychiatric research

“If we knew what we were doing, we wouldn’t call it research, would we?”

Albert Einstein