

Treatment Resistant Depression

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Conflicts of Interest

David L. Dunner, M.D. 1/08

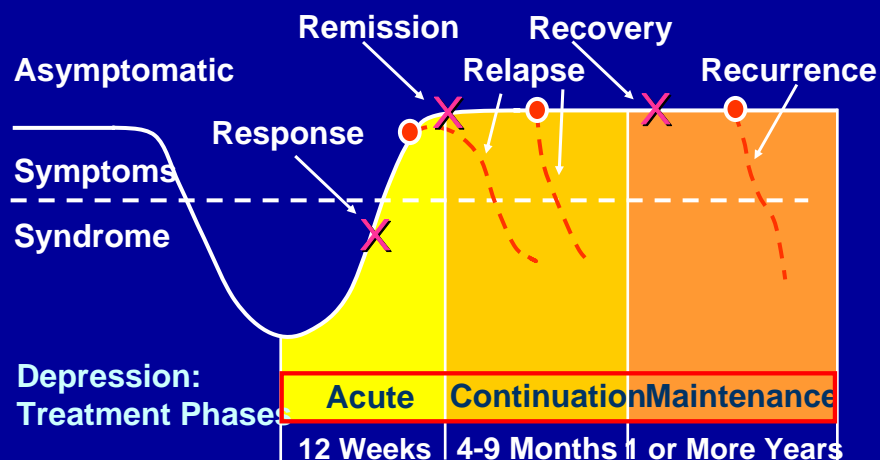
	Recent grant support	Consultant/Advisory Board	Speaker's Bureau
1. Eli Lilly	X	X	X
2. Pfizer	X	X	X
3. GlaxoSmithKline	X	X	X
4. Wyeth	X	X	X
5. BristolMyersSquibb	X	X	X
6. Organon			X
7. Forest	X	X	
8. Cyberonics	X		
9. Roche Diagnostics		X	
10. Cypress		X	
11. Corcept		X	
12. Janssen	X	X	
13. Novartis	X	X	
14. Shire		X	
15. Somerset		X	
16. Otsuka		X	
17. Healthcare Technology Sys		X	
18. Jazz Pharma		X	

What Are the Expected Response and Remission Rates for Depression?

- For patients diagnosed with major depression
 - 65%-75% will show clinically significant improvement acutely
 - 40%-50% will show complete recovery
 - 25%-35% will show only minimal improvement
- Treatment-resistant depression (TRD) may account for 30%-60 of patients diagnosed with depression

Frazer A. *J Clin Psychiatry*. 1997;58(suppl 6):9-25; Cadieux FR. *Am Fam Physician*. 1998;58:2059-2062.

Treatment Phases



Kupfer DJ. *J Clin Psychiatry*. 1991;52(suppl):28-34; AHCPR. Rockville, Maryland: U.S. Dept of Health and Human Services; 1993. Publication 93-0551.

Proposed TRD Staging: Levels of Resistance

- Stage I: Failure of at least 1 adequate trial of a major class of antidepressant
- Stage II: Stage I resistance plus failure of adequate trial of antidepressant in distinctly different pharmacologic class
- Stage III: Stage II resistance plus failure of adequate trial of tricyclic antidepressant (TCA)
- Stage IV: Stage III resistance plus failure of adequate trial of monoamine oxidase inhibitor (MAOI)
- Stage V: Stage IV resistance plus failure of course of bilateral electroconvulsive therapy (ECT)

Thase ME, Rush AJ. *J Clin Psychiatry*. 1998;(suppl 13):23-29.

Levels of Treatment Resistance

- Simple Minimal number of trials, low doses, brief duration, same class of medication
- Complicated Failure to respond to 3 or more adequate trials, may include augmentation

5 Ds of Treatment Resistance

- Diagnosis
- Dose
- Duration
- Drug mechanism of action
- Different treatment

Dunner DL, adapted from Csernansky and Hollister, 1986.

Characteristics of Treatment-Resistant Depression

- Higher frequency of suicide attempt
- Chronic depression
- Low utilization of ECT (18%)
- About 1/3 trials brief
- About 1/3 trials low dose
- About 1/3 misdiagnosed
- N=49, mean of 5 trials

Nelsen MR, Dunner DL. Psychiatr Clin North Am. 1993;16:541-566.

A Long-Term, Prospective, Naturalistic Study of Usual Standard-of-Care Treatment in Patients With Treatment-Resistant Depression (D-04)

Dunner DL, et al. Prospective, long-term, multicenter study of the naturalistic outcomes of patients with treatment-resistant depression. J Clin Psychiatry 2006; 67:688-695.

Supported by a research grant from Cyberonics, Inc.

Long-Term Study of Treatment- Resistant Depression

Purpose

- Evaluate clinical outcomes
- Evaluate cost utilization

Long-Term Study of Treatment-Resistant Depression (Cont'd)

Methods

- 14 clinical centers
- 127 patients
- Nonresponse to 2 to 6 treatments (current MDE)
- Up to 5 medications at baseline
- Exclude: atypical depression, psychotic disorders
- Usual care for 2 years
- Assessments: Baseline, Q 3 months

MDE = major depressive episode.

Long-Term Study of Treatment-Resistant Depression: Assessments

- IDS-SR
- HAMD₂₄
- HSUPCA*

*Health Service Utilization and Productive Capacity Assessment.

Long-Term Study of Treatment-Resistant Depression: Demographics

Mean age (y)	46
% Female	69
% Caucasian	88
% Unipolar	87
% Recurrent	86
% Chronic (current episode)	66
Duration of current MDE (mos)	68.5
Mean age of onset (y)	21
1 or more suicide attempts, %	35
N=127	

Long-Term Study of Treatment-Resistant Depression

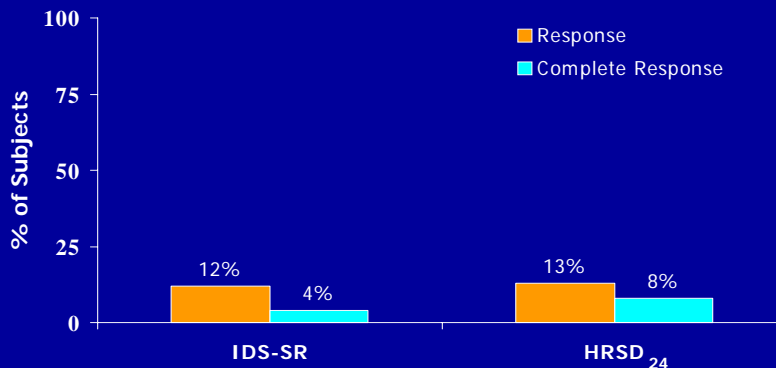
- Treatment History
- Number of failed adequate trials, current MDE 3.2
- ECT ever, 26%
- ECT current MDE, 12%
- Patients ever hospitalized, 57%

Treatments

	Baseline* (127 patients)		1-Year (119 patients)	
	N	(%)	N	(%)
Heterocyclics/TCAs	49	(38.5)	18	(15.1)
SSRIs	116	(91.3)	73	(61.3)
MAOIs	21	(16.9)	10	(8.4)
Other antidepressants	126	(99.2)	95	(79.8)
Anticonvulsants	60	(47.2)	58	(48.7)
Benzodiazepines	66	(51.9)	67	(56.3)
Stimulants	29	(22.8)	23	(19.3)
Atypical antipsychotics	44	(34.6)	38	(31.9)
Nonatypical antipsychotics	6	(4.7)	4	(3.4)
ECT	15	(12)	17	(14)

* Treatment for the current major depressive episode

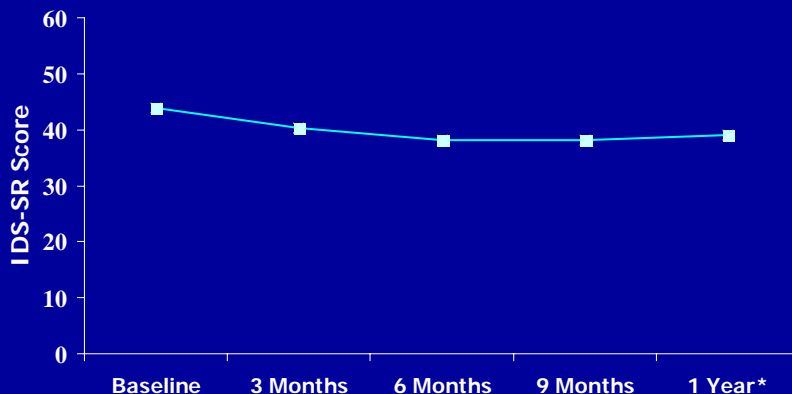
IDS-SR and HRSD₂₄ Response at 1 Year (n = 112)



Response defined as $\geq 50\%$ decrease in total raw scores between baseline and 1 year.

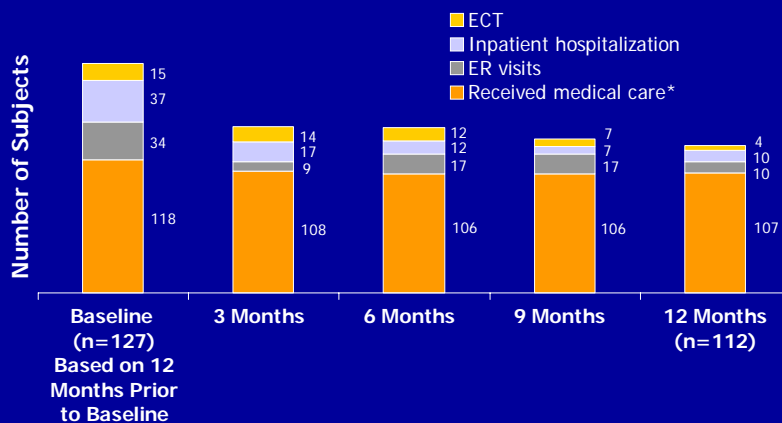
Complete response defined as HRSD raw score ≤ 9 and IDS-SR raw score ≤ 14 .

IDS-SR Mean Ratings Over 12 Months



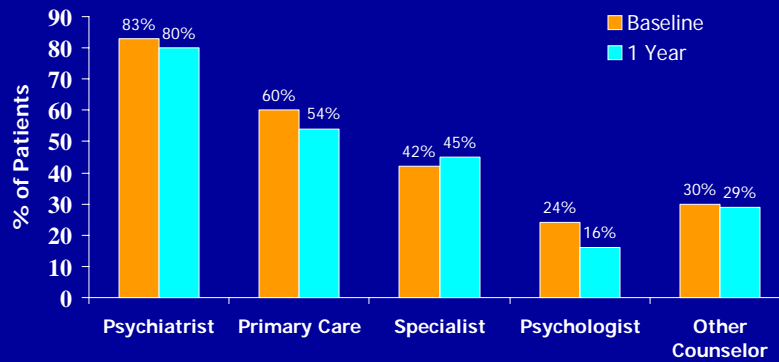
Sustained response defined as ≥ 50 improvement in IDS-SR scores at both 9 and 12 months. At 1 year, only 5% of patients (5/112) were considered sustained responders.

HSUPCA Summary of Medical Care

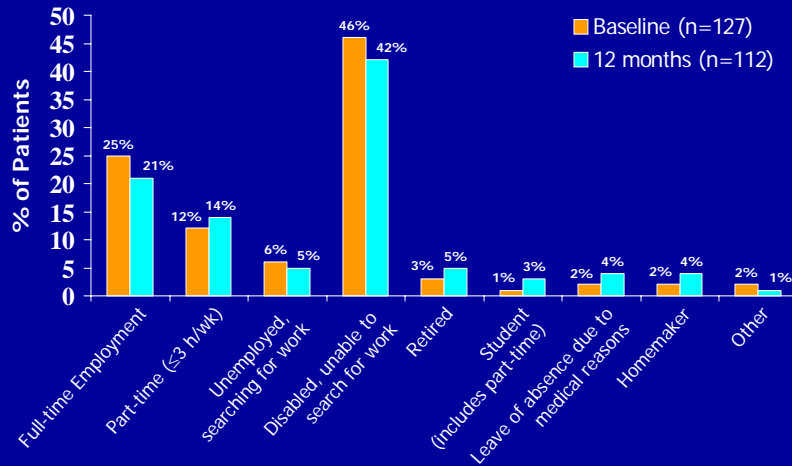


*Doctor visits other than for the study, emergency room visits, x-rays, surgery, and/or hospitalizations.

Percentage of Patients Utilizing Health Care Services



HSUPCA Productive Capacity



Long-Term Study of Treatment-Resistant Depression

Conclusions

- Poor response rates with usual standard-of-care treatment
 - (Response 12%-13%; Complete response 4%-8%)
 - Response not sustained
- Extensive health care utilization
- Little change in productivity measures

Treatment Resistant Depression: Diagnosis

- Primary-secondary (co-morbidity)
- Severity
- Subtyping (atypical, melancholic, psychotic)
- Course (recurrent, chronic, “double”)
- Medical (endocrine, tumor, medications)

Treatment Resistant Depression: Dose, Duration

- At least double starting doses for newer antidepressants (SSRIs may have flat dose response curves)
- At least 8-12 weeks at maximal tolerated dose

Treatment Resistant Depression: Drug

- What is the putative mechanism of action of the drug being used?
- Is it treatment resistance or treatment intolerance?
- Does the drug have different MOA at different doses?

Treatment Resistant Depression: Different Treatment

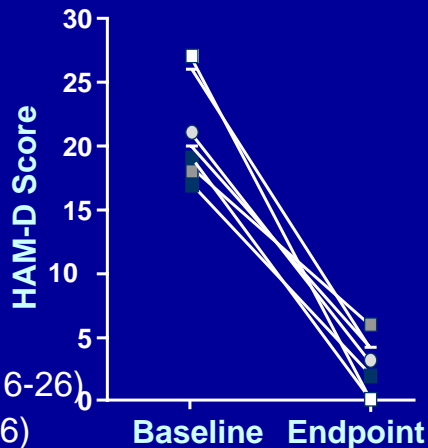
- Augment
- Switch

Treatment Resistant Depression: Augmentation

- Lithium
- Thyroid (T3)
- Atypical Antipsychotic
- Benzodiazepine
- ?Lamotrigine, buspirone
- Another antidepressant
- Not useful: pindolol, tryptophan, modafinil

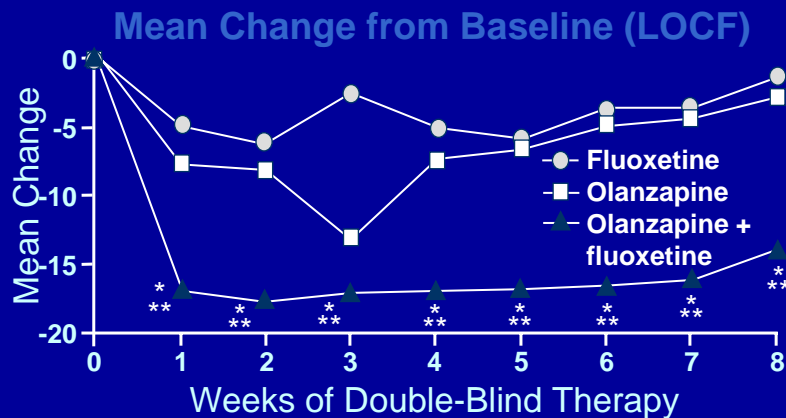
Risperidone Augmentation of SSRIs in Major Depression

- 8 patients with major depression
- Ages 36-75
- Failure to 1 SSRI
 - Fluoxetine N=5
 - Paroxetine N=3
- HAM-D
 - Baseline mean = 20.5 (16-26)
 - Endpoint mean = 2.4 (0-6)
 - Time to response: 1-7 days



Ostroff RB, Nelson JC. J Clin Psychiatry. 1999;60(4):256-259

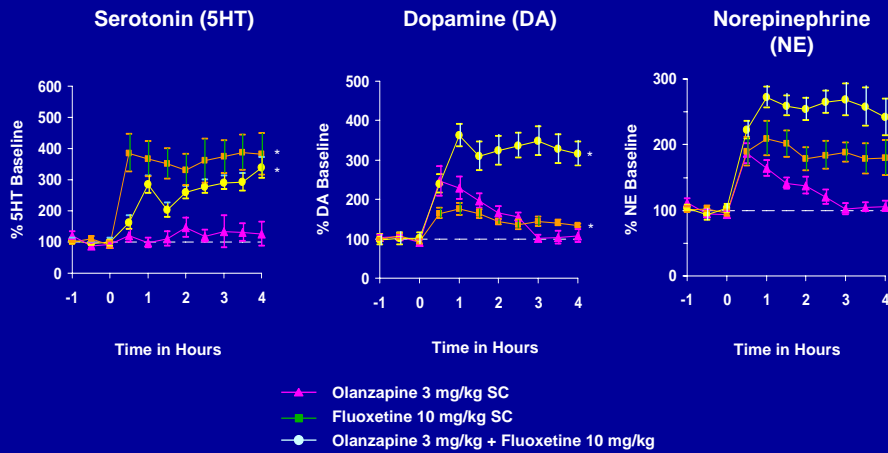
MADRS Total: Acute Therapy



- OLZ + FLX yielded a rapid and sustained response in many patients

*p<0.05 vs. fluoxetine; **p<0.05 vs. olanzapine; MADRS = Montgomery-Asberg Depression Rating Scale; Mean modal dose: FLX 52.0 ± 14.0 mg/day; OLZ 12.5 ± 5.3 mg/day; OLZ + FLX 13.5(10.3) + 52.0(4.1) mg/day; Mean modal dose: OLZ + FLX 10.7 + 47.3 mg/day; Shelton RC et al. Am J Psychiatry. 2001;158(1):131-134

Synergistic Effects of Olanzapine and Fluoxetine in Rat Prefrontal Cortex



*p<0.05 vs baseline.

Zhang W et al. 2000.

Treatment Resistant Depression: Atypical Antipsychotic Augmentation

- SSRIs
 - Paroxetine
 - Fluoxetine
 - Sertraline
 - Citalopram
 - Venlafaxine (?Duloxetine)
- Atypical neuroleptics
 - Aripiprazole*
 - Risperidone
 - Olanzapine
 - Ziprasidone
 - Olanzapine-Fluoxetine Combination

*FDA approved

Treatment Resistant Depression: Switch

- SSRI-SSRI
- SSRI-SNRI (Ven, Dulox), SSRI-bupropion
- SSRI-Venlafaxine +bupropion/Ven + Mirt
- ECT
- MAOI
- Other
- Psychotherapy

Consultation

Treatment Resistant Depression: New Treatments

- “High Dose” RUL ECT
- Vagus Nerve Stimulation (VNS)
- Transcranial Magnetic Stimulation (rTMS)
- Deep Brain Stimulation
- New Medications (Agomelatine, Gepirone, Desvenlafaxine, others)
- STAR*D Program

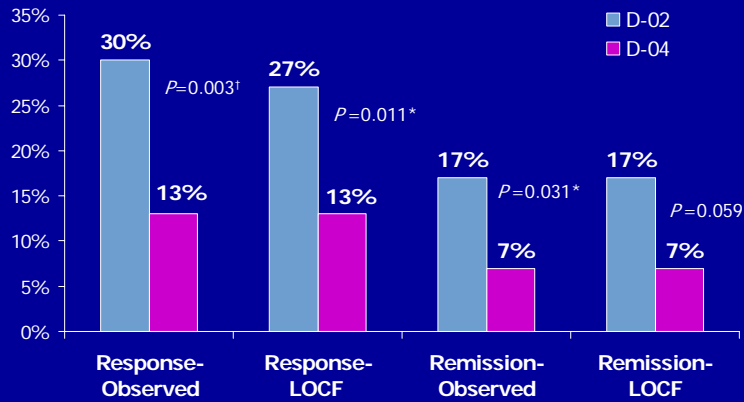
VNS Therapy Pulse Generator & Lead

- Implanted in more than 22,000 patients worldwide
- Pacemaker-like pulse generator
- Model 102 for use with a single-pin lead
- 6.9 mm thick (33% thinner than Model 101)
- Weighs 25 g (34% lighter than Model 101)

Vagus Nerve Stimulation (VNS) Therapy

- Mild electrical pulses applied to the left vagus nerve in the neck for transmission to the brain
- Intermittent stimulation
 - 30 sec on/5 min off
 - 24/7
- Magnetic empowerment
 - On-demand stimulation
 - Acute side effects control
- Simple in-office programming (dosing) by treating physician
- 100% patient adherence

D-02 vs D-04: 12-Month HRSD₂₄ Response and Remission Rates



*Significant at the <0.050 level. [†]Significant at the <0.010 level.
 D-02 Observed n=180, LOCF n=204
 D-04 Observed n=104, LOCF n=104



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