Can Clinicians Improve Antidepressant Remission Rates with Better Algorithms?

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APA GUIDELINE-BASED ANTIDEPRESSANT SELECTION ALGORITHMS

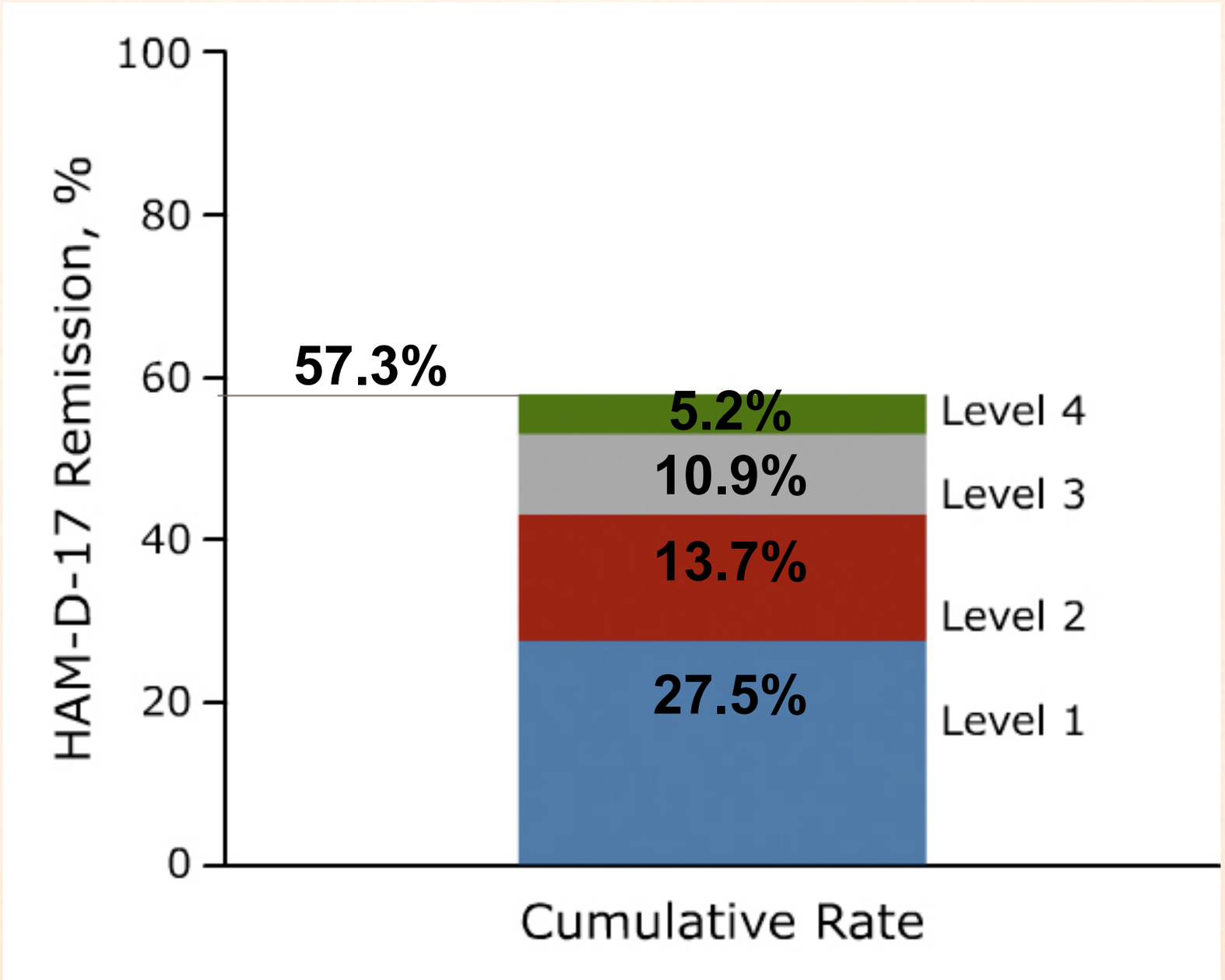
STAR*D ALGORITHM

* LEVEL I ALL PATIENTS USE CITALOPRAM INITIALLY.

* LEVEL II SWITCH TO BUPROPION (SUSTAINED-RELEASE), COGNITIVE THERAPY, SERTRALINE, VENLAFAXINE OR AUGMENT WITH BUPROPION (SUSTAINED-RELEASE), BUSPIRONE, COGNITIVE THERAPY.
* LEVEL IIA (ONLY FOR THOSE RECEIVING COGNITIVE THERAPY IN LEVEL 2) BUPROPION (SUSTAINED-RELEASE) OR VENLAFAXINE (EXTENDED-RELEASE)
* LEVEL III SWITCH TO MIRTAZEPINE OR NORTRIPTYLINE OR AUGMENT WITH LITHIUM OR TRIIODOTHYRONINE (ONLY WITH BUPROPION [SUSTAINED-RELEASE]), SERTRALINE, VENLAFAXINE (EXTENDED-RELEASE).
* LEVEL IV SWITCH TO TRANYLCYPROMINE OR MIRTAZEPINE COMBINED WITH VENLAFAXINE (EXTENDED RELEASE).

Rush et al. Arch Gen Psychiatry 2008; 65:870-80

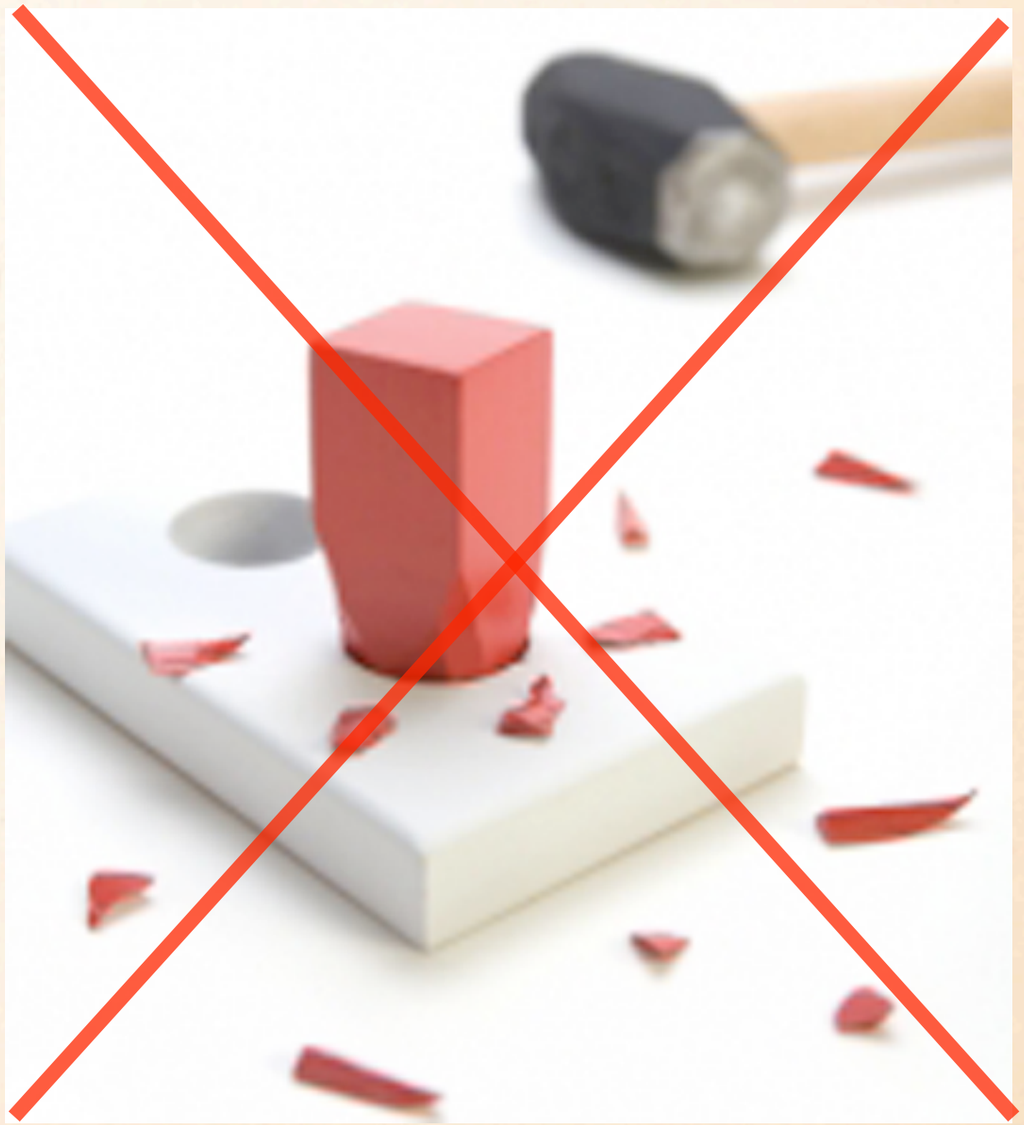
STAR*D REMISSION RATES



Rush et al. Am J Psychiatry 2006;163:1905-17

GETTING IT RIGHT THE FIRST TIME

- CLINICIANS HAVE THE BEST CHANCE OF GETTING PATIENTS INTO REMISSION WITH THE FIRST TREATMENT TRIAL, SO MATCHING THE FIRST-LINE SELECTION IN A TREATMENT ALGORITHM TO THE INDIVIDUAL PATIENT'S NEEDS MUST BE CONSIDERED CAREFULLY. – MICHAEL E. THASE



Thase, M. Treating Major Depression: Antidepressant Algorithms, http://www.cmeinstitute.com/psychlopedia/depression/3cmdd/sec1/section.asp

INDIVIDUALIZED ALGORITHMS

- DERIVED FROM STUDIES THAT DISTINGUISH PATIENTS BY EMPIRICALLY-DERIVED SYMPTOM PROFILES
- USE MEASUREMENT-BASED CASE MANAGEMENT TO SELECT INITIAL TREATMENT AND MAINTAIN REMISSION
- MAY ANTICIPATE ENDOGENOTYPIC DIFFERENCES BETWEEN DEPRESSED PATIENTS

IMPAIRED NEUROTRANSMISSION AND REDUCED NEURAL ADAPTABILITY

↓SEROTONIN

IMPAIRED MODULATION

Anxiety
Irritability
Hostility
Impulsivity
Agitation
Hypochondriasis
Suicidality

↓NOREPINEPHRINE

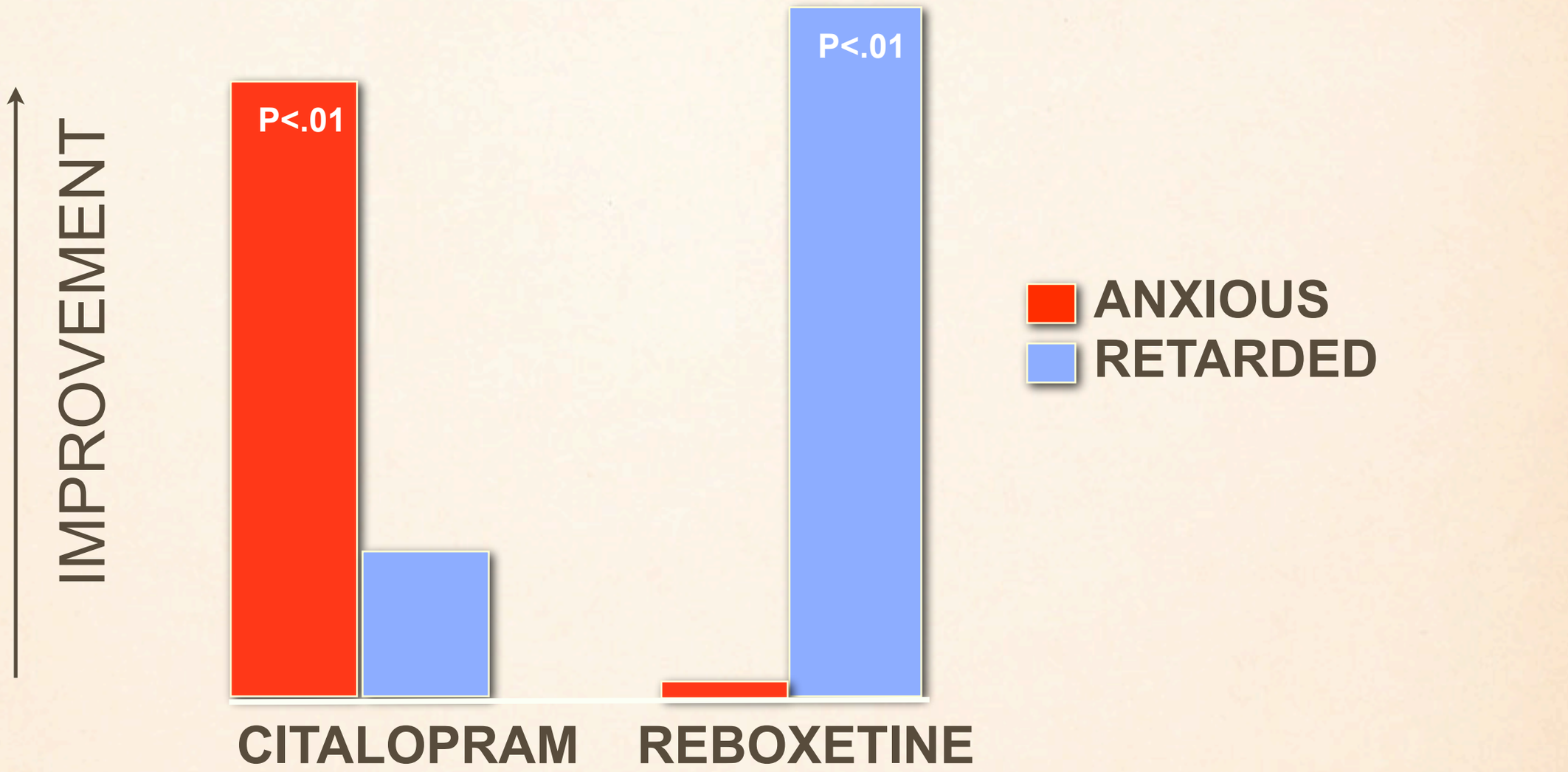
IMPAIRED ACTIVATION

Fatigue
Apathy
Anhedonia
Hypersomnia
Lack of initiative
Inability to concentrate
Decreased productivity

DEPRESSION

↓DOPAMINE

SSRI MORE EFFECTIVE IN ANXIOUS DEPRESSION; NRI BETTER IN PSYCHO-MOTOR RETARDED DEPRESSION



A 16 WEEK DOUBLE-BLIND STUDY OF POST-STROKE DEPRESSED PATIENTS; IMPROVEMENT WAS MEASURED USING A 26-SYMPTOM SUBTYPING SCALE

RAMPELLO ET AL. PREDICTION OF THE RESPONSE TO CITALOPRAM AND REBOXETINE IN POST-STROKE DEPRESSED PATIENTS. PSYCHOPHARMACOLOGY (BERL) 2004; 173:7378

THREE FUNCTIONAL SUBTYPES OF DEPRESSION

SUBTYPE	TRADITIONAL TERMS	OPTIMAL TREATMENT
DEMODULATED	anxious, agitated, hostile, hypochon-driacal	serotonergic
DEACTIVATED	psychomotor-retarded, blunted, apathetic	catecholaminergic
MIXED	melancholic, atypical, resistant	dual-mechanism

METZNER R, APA ANNUAL MEETING, 2000

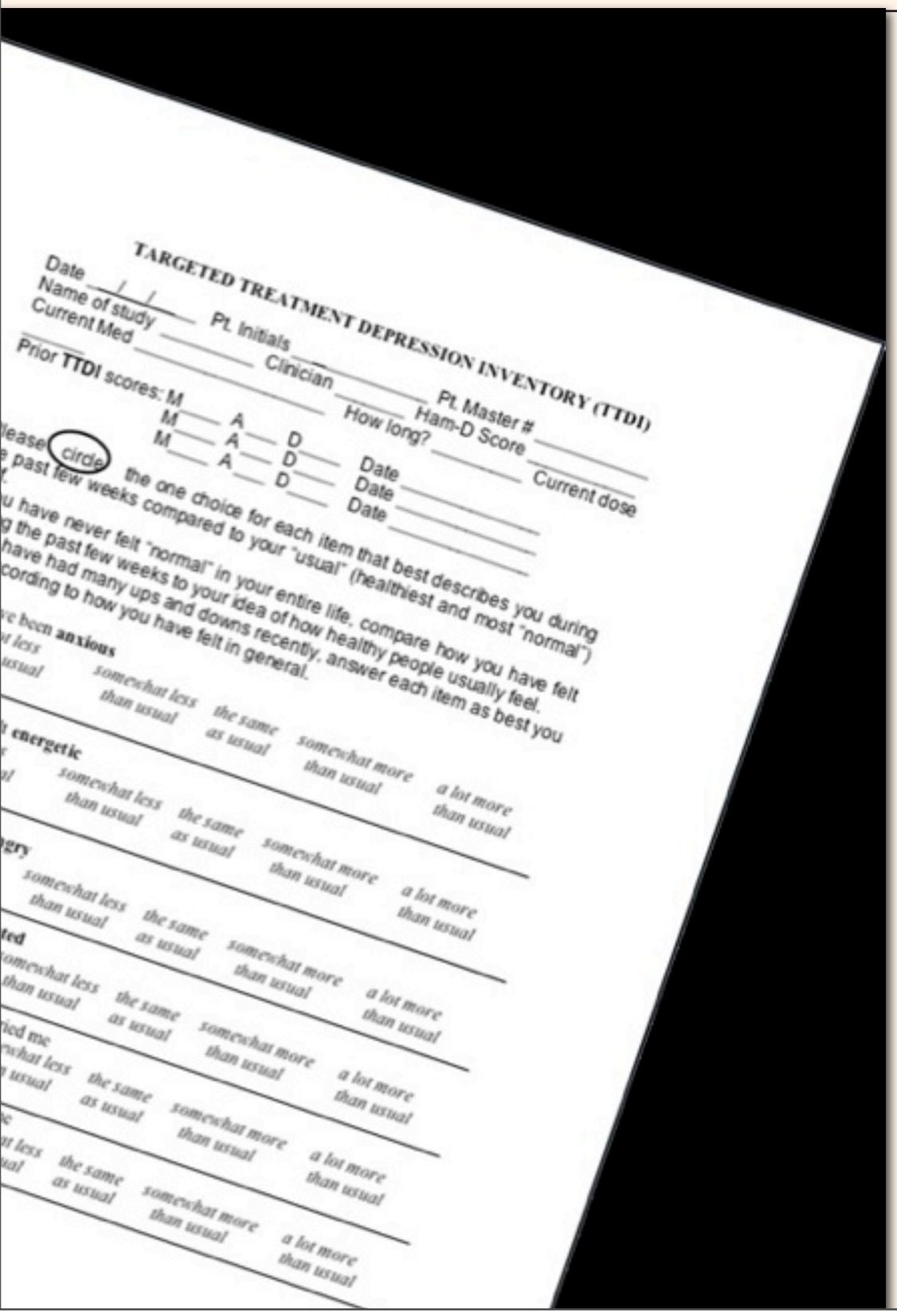
DSM-IV CRITERIA FOR MAJOR DEPRESSION

- PERSISTENT DEPRESSED MOOD (+)(-)
- ANHEDONIA (-)
- WEIGHT LOSS(+) OR GAIN (-)
- INSOMNIA (+) OR HYPERSOMNIA (-)
- AGITATION (+) OR RETARDATION (-)
- EXCESSIVE WORTHLESSNESS OR GUILT (+)
- DIMINISHED COGNITIVE FUNCTION (-)
- SUICIDAL IDEATION (+)

(+)=DEMODULATED

(-)=DEACTIVATED

THE TTDI: A METHOD FOR INDIVIDUALIZING ANTIDEPRESSANT TREATMENT


TARGETED TREATMENT DEPRESSION INVENTORY (TTDI)

Date ___/___/___ Pt. Initials ___ Pt. Master # ___

Name of study ___ Clinician ___ Ham-D Score ___

Current Med ___ How long? ___ Current dose ___

Prior TTDI scores: M___ A___ D___ Date ___

M___ A___ D___ Date ___

M___ A___ D___ Date ___

lease circle the one choice for each item that best describes you during
e past few weeks compared to your "usual" (healthiest and most "normal")
u have never felt "normal" in your entire life, compare how you have felt
g the past few weeks to your idea of how healthy people usually feel.
have had many ups and downs recently, answer each item as best you
cording to how you have felt in general.

e been **anxious**

	somewhat less than usual	the same as usual	somewhat more than usual	a lot more than usual
t less usual				

energetic

	somewhat less than usual	the same as usual	somewhat more than usual	a lot more than usual
l				

gry

somewhat less than usual	the same as usual	somewhat more than usual	a lot more than usual

ted

somewhat less than usual	the same as usual	somewhat more than usual	a lot more than usual

ied me

what less usual	the same as usual	somewhat more than usual	a lot more than usual

e

t less ual	the same as usual	somewhat more than usual	a lot more than usual

- THE TARGETED TREATMENT OF DEPRESSION INVENTORY (TTDI) IS A SELF-ADMINISTERED, COMPUTER-SCORED 17-ITEM QUESTIONNAIRE BASED ON THE TRIPARTITE MODEL OF CLARK AND WATSON.

– CLARK LA AND WATSON D. TRIPARTITE MODEL OF ANXIETY AND DEPRESSION: PSYCHOMETRIC EVIDENCE AND TAXONOMIC IMPLICATIONS.J ABN PSYCHOLOGY 1991; 100:316-336

- METZNER RJ. METHOD FOR THE TARGETED TREATMENT OF DEPRESSION. US PATENT DOCUMENT #20040015055, APPROVED AS AMENDED 5/4/09; HTTP://PATFT.USPTO.GOV/

THE TTDI: A METHOD FOR INDIVIDUALIZING ANTIDEPRESSANT TREATMENT

- TWO INDEPENDENT SUBSCALES – MODULATION (M)  AND ACTIVATION (A)  FOR DIAGNOSING SUBTYPES AND GUIDING CHOICE OF ANTIDEPRESSANTS

- SINGLE DEPRESSION SCORE (D= M+A)  TO MEASURE OVERALL SEVERITY

TTDI ALGORITHM

DEMODULATED

YES

DEACTIVATED

YES

M IXED
USE
DUAL
MECHANISM
REGIMEN

NO

DEMODULATED

USE SSRI

NO

DEACTIVATED

YES

DEACTIVATED

USE NDRI

TTDI ALGORITHM: PRELIMINARY DATA

- FROM 1985 TO 2000 DEPRESSED OUTPATIENTS (N=1,035) RECEIVED NON-SELECTIVE (TCA OR MAOI) OR SELECTIVE ANTIDEPRESSANTS
- SELECTIVE ANTIDEPRESSANTS WERE INDIVIDUALIZED BASED ON CLINICAL INTERVIEWS:
  - SEROTONERGIC (SSRI) FOR DEMODULATED PATIENTS
  - CATECHOLAMINERGIC (BUPSR) FOR DEACTIVATED
  - DUAL MECHANISM (VLFXR, MRT OR SSRI+BUPSR) FOR MIXED
- NON-SELECTIVELY TREATED SAMPLE (N=55) HAD 65% CLINICAL IMPROVEMENT (CGI<3)
- INDIVIDUALIZED TREATMENT SAMPLE (N=100) HAD 96% CLINICAL IMPROVEMENT

METZNER R, APA ANNUAL MEETING, 2000

TTDI STUDY: RECRUITMENT

- LECTURES ON THE TTDI ALGORITHM WERE GIVEN AT OVER FIVE HUNDRED LOCATIONS THROUGHOUT THE U.S. AND PUERTO RICO STARTING IN MAY, 2000.

TTDI STUDY: WEBSITE

- FROM SEPTEMBER, 2005 TO JUNE, 2008 PROFESSIONALS IN 80 PRIMARY CARE AND SPECIALTY SETTINGS VOLUNTARILY ACCESSED THE TTDI USING A SECURE WEBITE (WWW.TTDI.INFO)

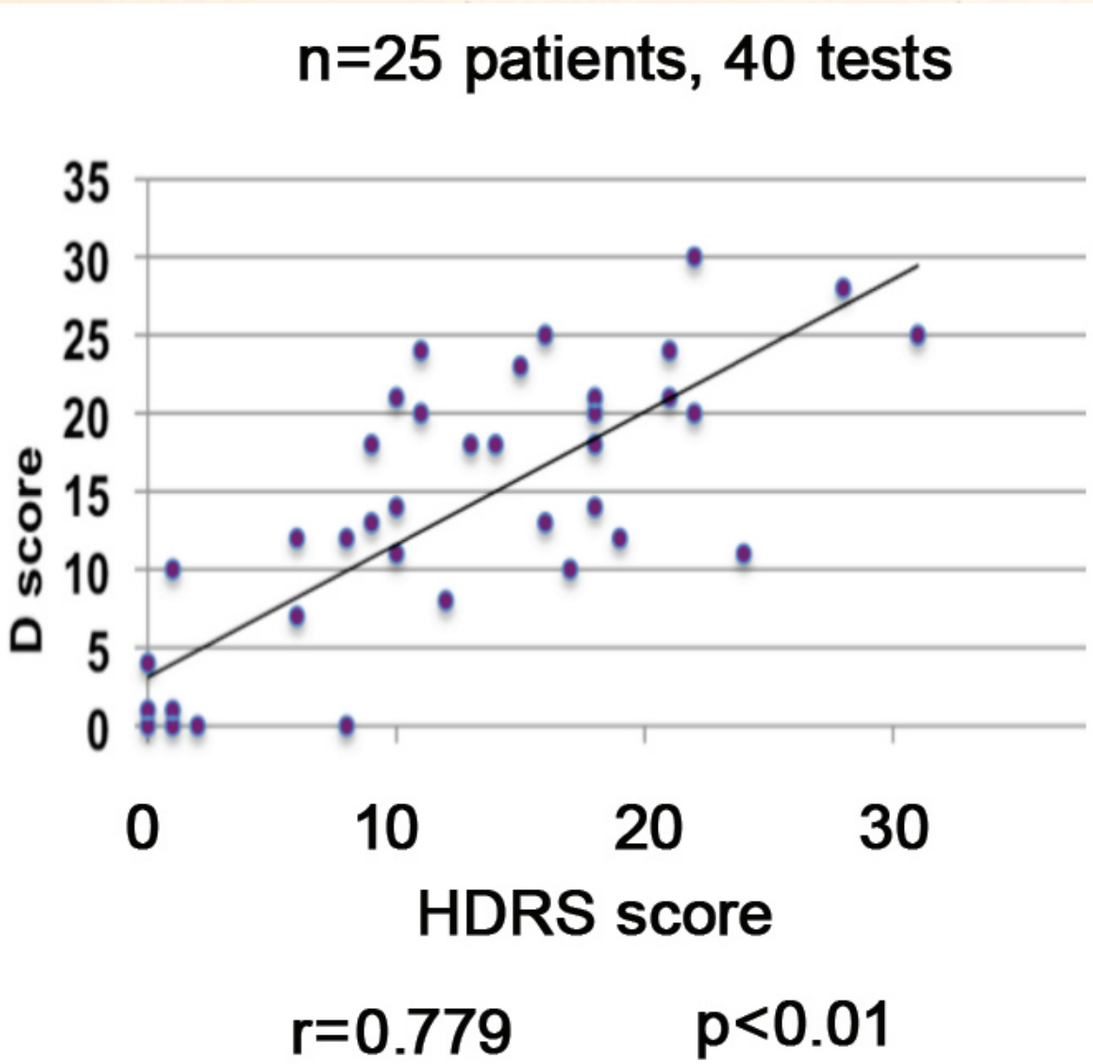
- THE SITE PROVIDED FREE ACCESS TO TTDI QUESTIONNAIRES, ONLINE SCORING, AN ANONYMIZING DATABASE AND TECHNICAL SUPPORT.

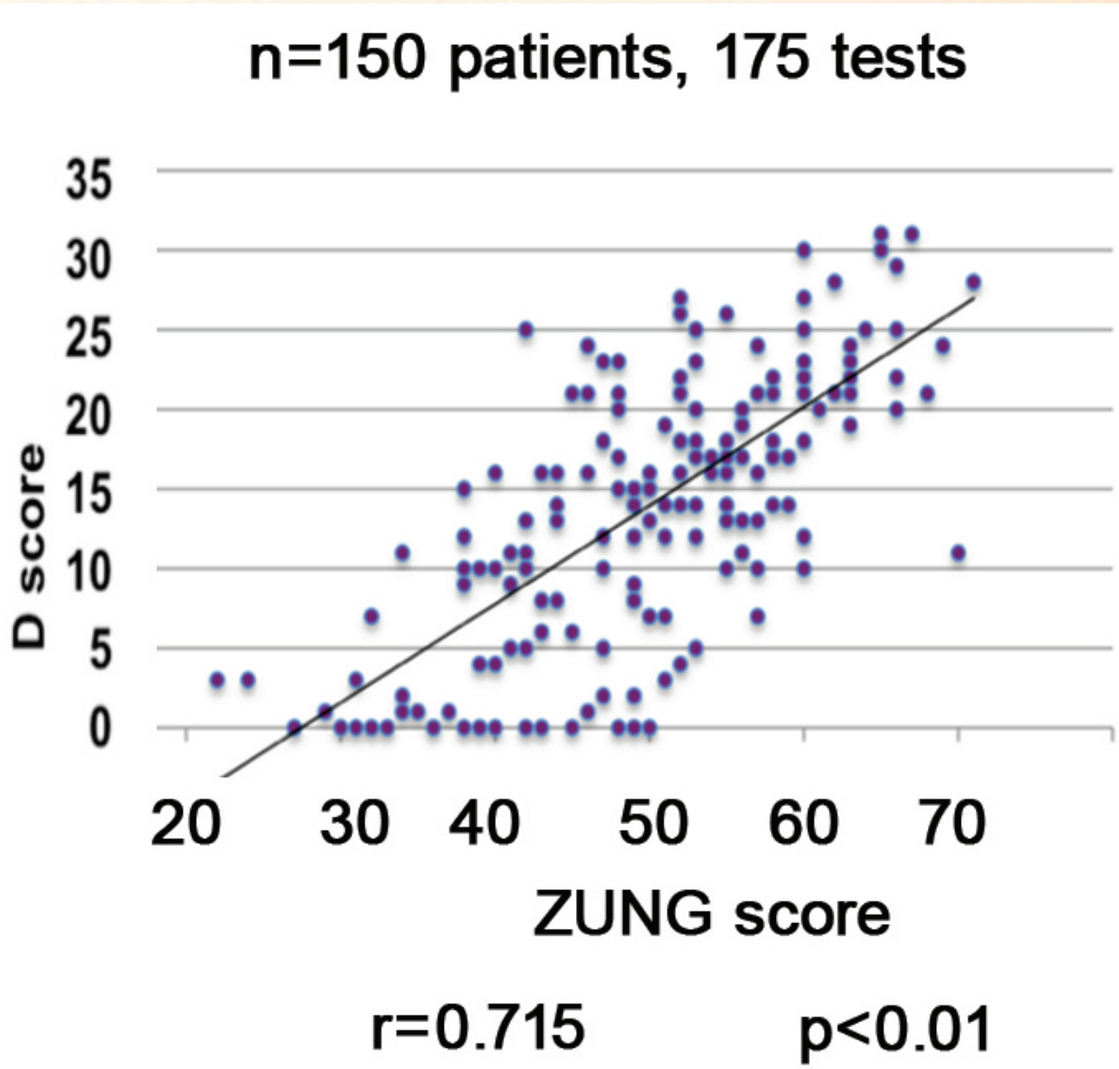
- HIPAA GUIDELINES WERE OBSERVED TO PROTECT PATIENT PRIVACY.

- A SAMPLE OF PATIENTS WAS ALSO RATED CONCURRENTLY WITH THE HAMILTON DEPRESSION RATING SCALE (HDRS), THE ZUNG SELF-RATED DEPRESSION SCALE (SDS) AND THE TTDI.

TTDI STUDY RESULTS: CONVERGENT VALIDITY

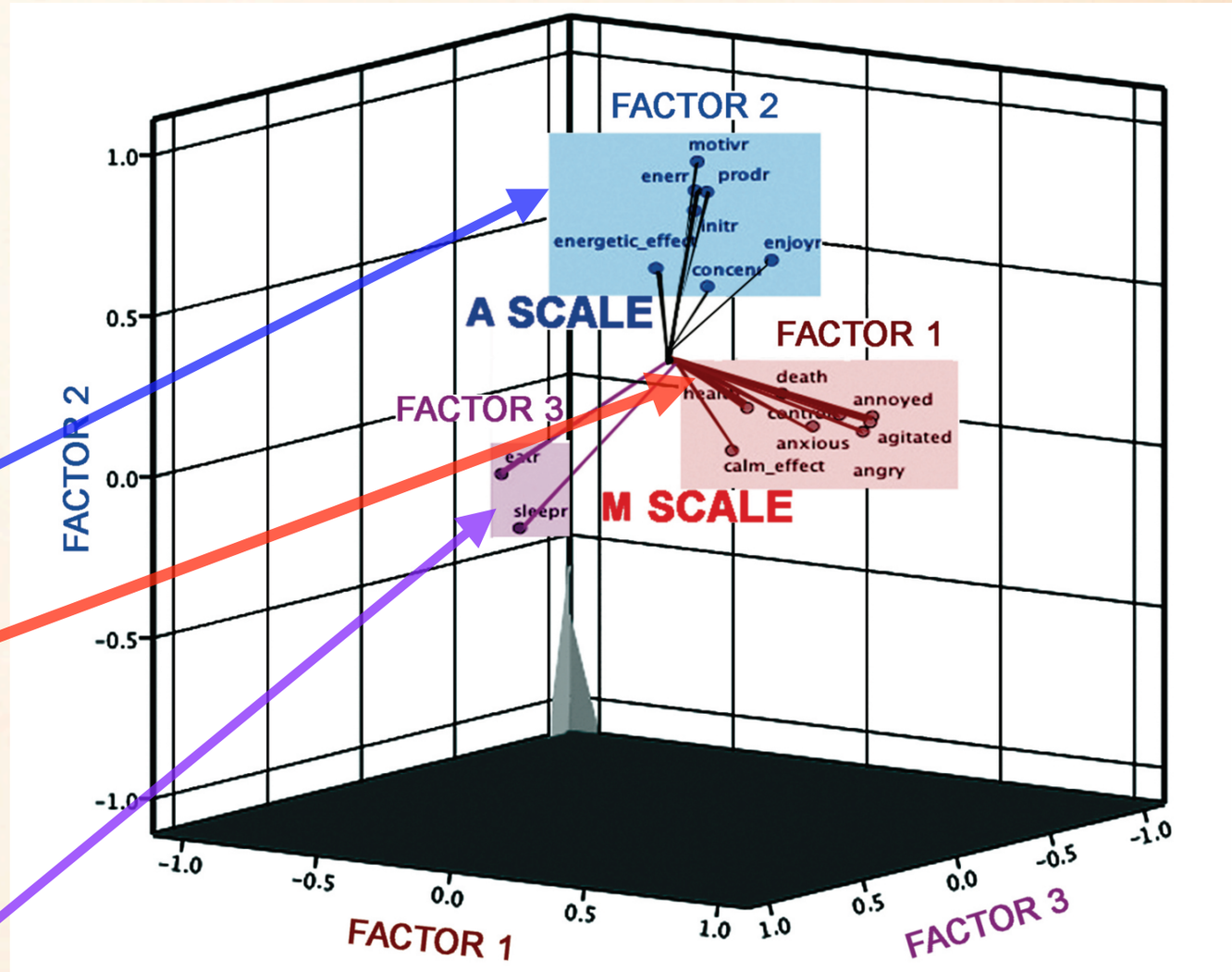
TTDI SCORES CORRELATED SIGNIFICANTLY WITH BOTH HDRS AND ZUNG SDS SCORES (P<0.01)





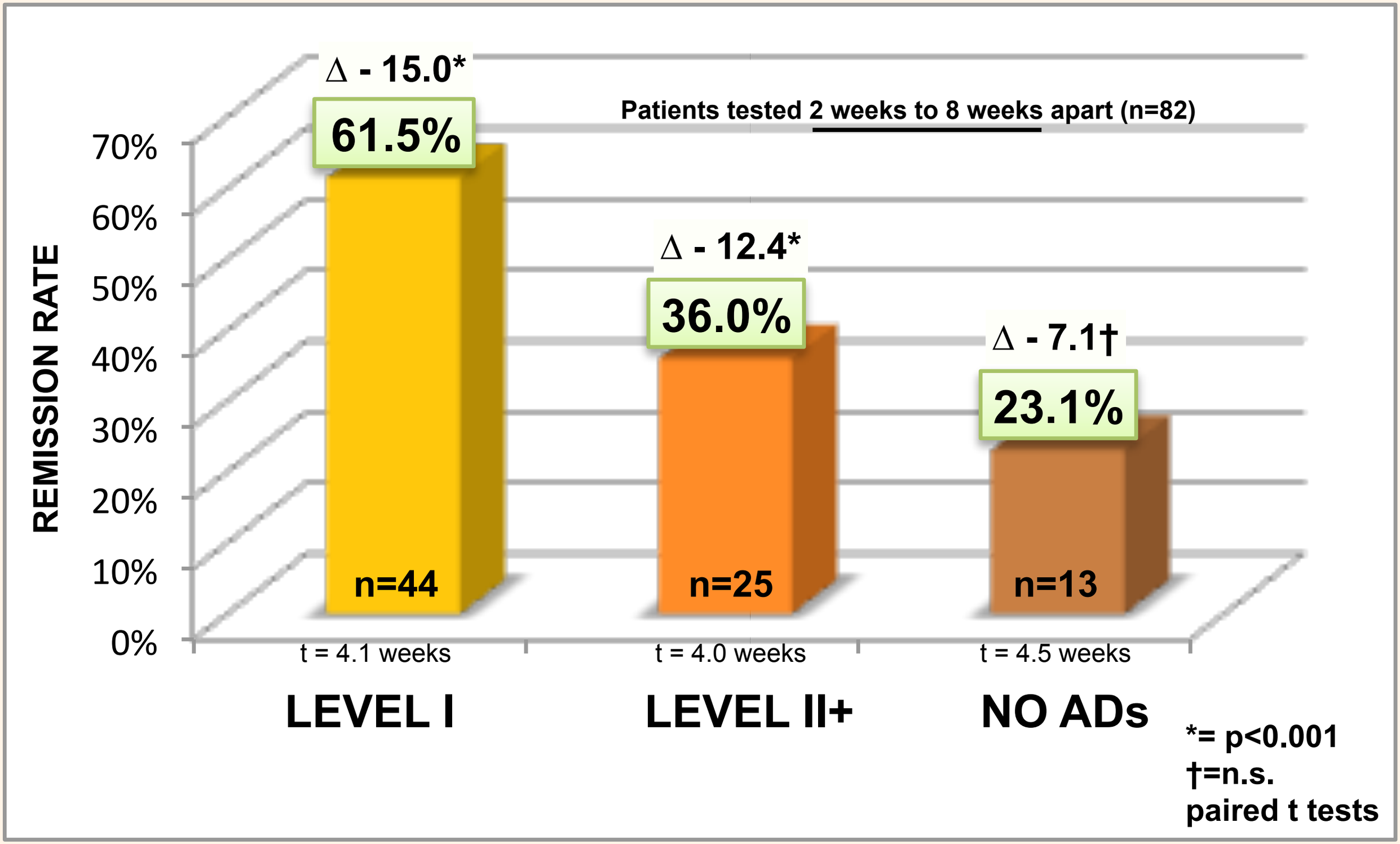
TTDI STUDY RESULTS: FACTOR ANALYSIS & SCALE RELIABILITY

FACTOR ANALYSIS REVEALED TWO PRINCIPLE FACTORS WITH NEARLY EQUAL ROTATED PERCENTS OF VARIANCE (21.3% AND 20.1%) CORRESPONDING EXACTLY TO THE **DEACTIVATION (A)** AND **DEMODULATION (M)** SCALE ITEMS, MINUS THE SLEEP AND APPETITE MEASURES WHICH FORMED A THIRD LESS PROMINENT FACTOR (3.8%)



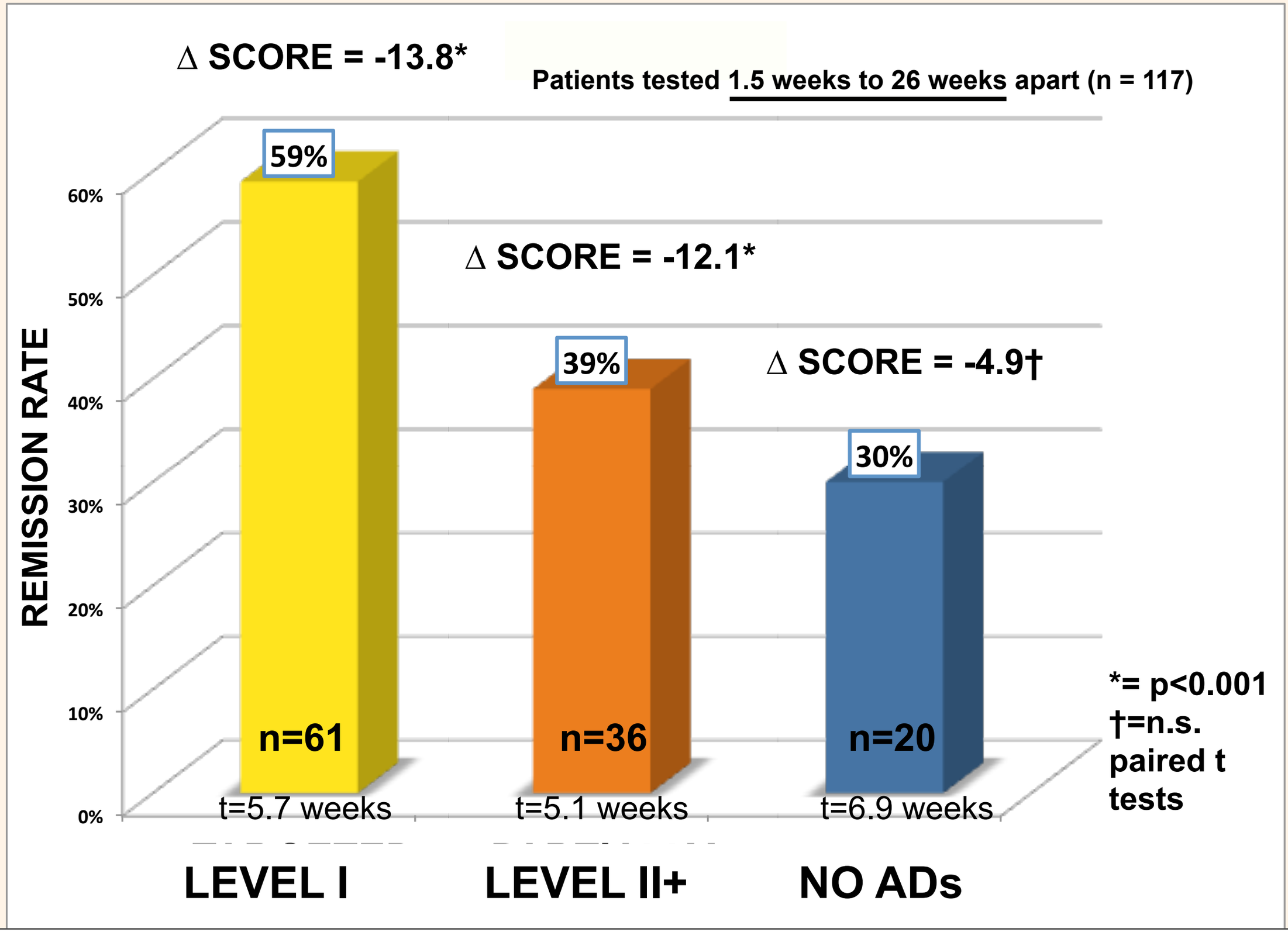
CRONBACH ALPHA **RELIABILITY** WAS HIGH (0.770 FOR BOTH A AND M SCALES AND 0.880 & 0.829, RESPECTIVELY, WHEN FACTOR 3 ITEMS WERE EXCLUDED)

TTDI STUDY RESULTS: REMISSION RATES AND SCORE CHANGES -- after 2 to 8 weeks



Metzner and Ho, unpublished data, August, 2008

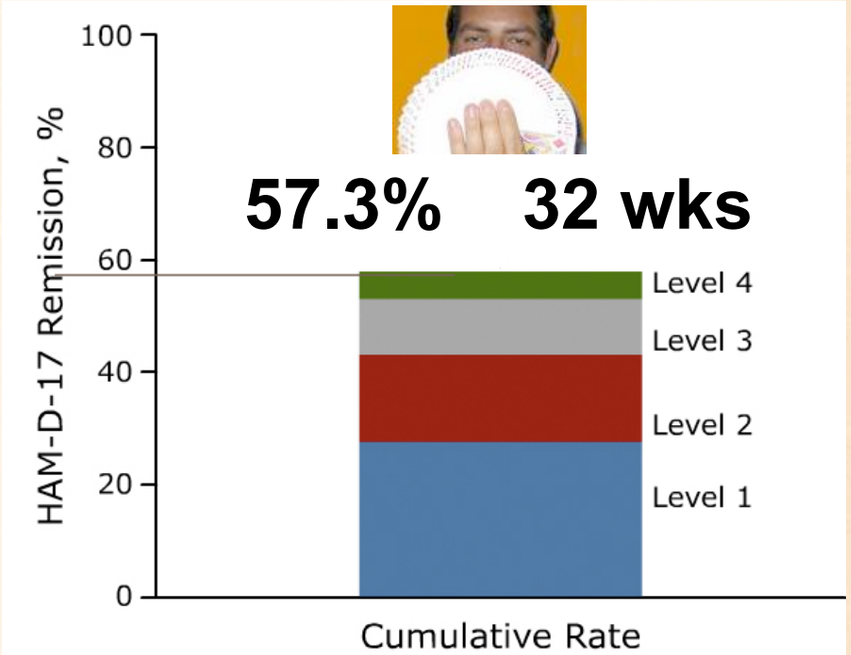
TTDI STUDY RESULTS: REMISSION RATES AND SCORE CHANGES -- after 1.5 to 26 weeks



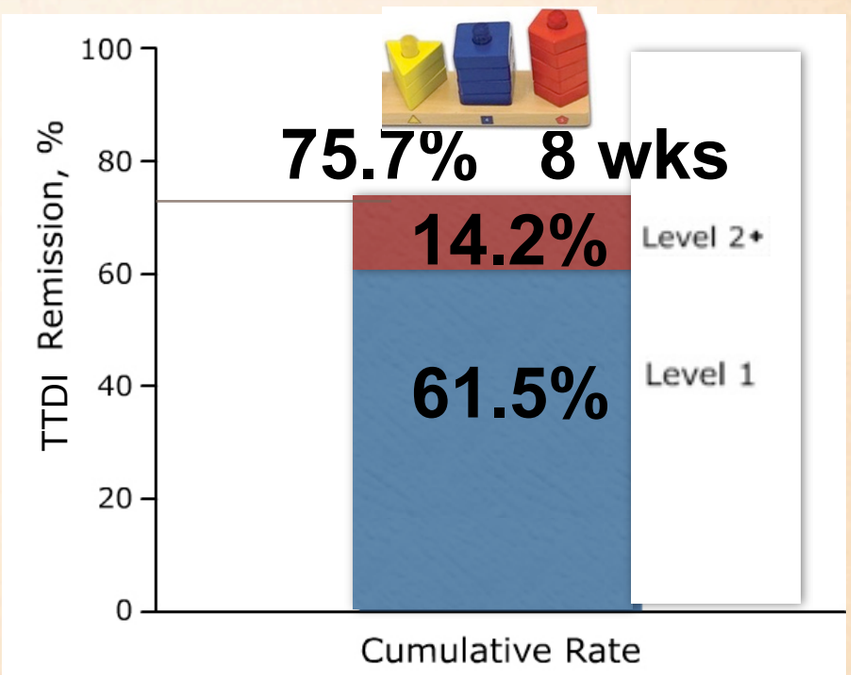
COMPARING RESULTS

The STAR*D patients achieved a cumulative remission rate of 57.3% (HDRS) after 4 treatment levels lasting about 32 weeks .

Rush et al. Am J Psychiatry 2006;163:1905-17



combining the TTDI level 1 patients' remission rate of 61.5% with the 14.2% rate associated with level 2+ patients produced a hypothetical cumulative remission rate of 75.7% after two treatment periods averaging a total of 8.1 weeks.



DO INDIVIDUAL SYMPTOMS PREDICT REMISSION RATES?

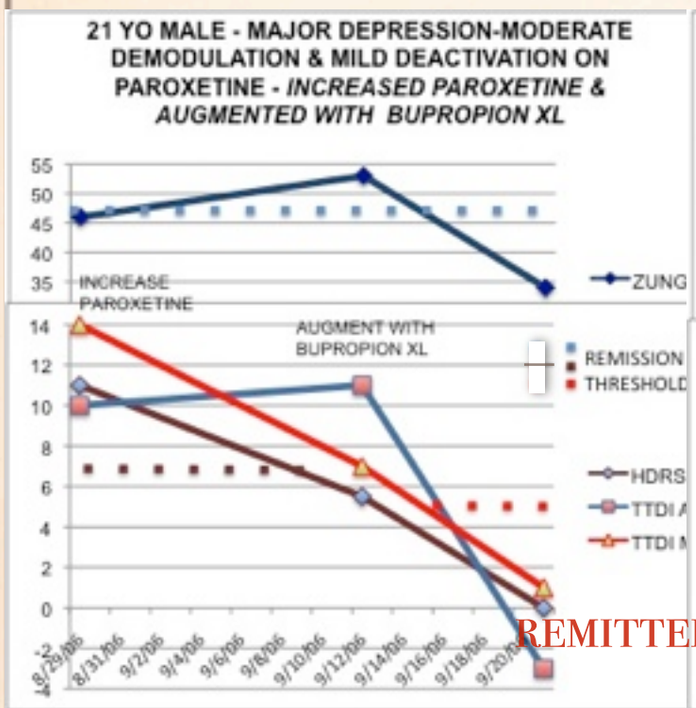
- DESPITE THE HIGH REMISSION RATE ACHIEVED BY WEIGHING COMBINATIONS OF TTDI RESPONSES IN RECOMMENDING ANTIDEPRESSANTS, OUR ANALYSIS OF THOSE ITEMS ALONE USING LOGISTICAL REGRESSION DID NOT DEMONSTRATE SIGNIFICANT PREDICTIVE VALUE FOR ANY OF THEM.

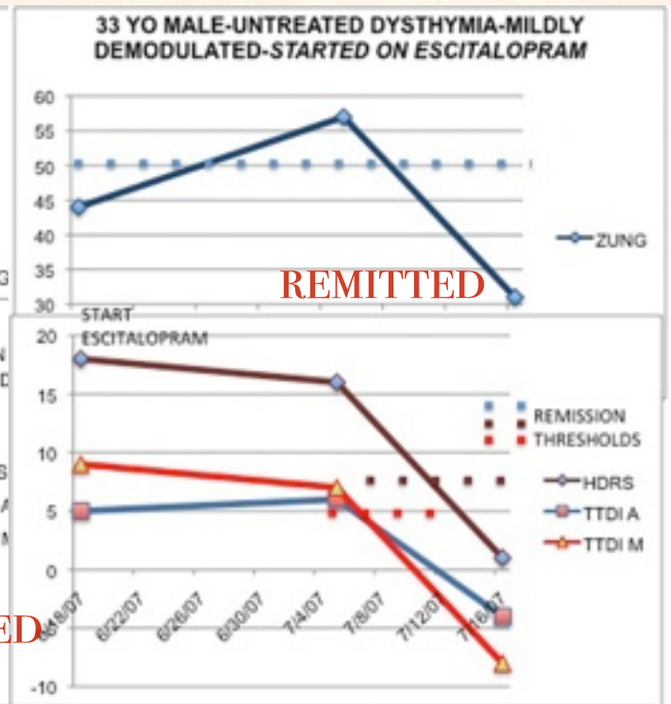
- CLINICAL STUDIES ARE, AS A RULE, STATISTICALLY UNDERPOWERED FOR REVEALING SIGNIFICANT EFFECTS OF INDIVIDUAL ITEMS ON SUSCEPTIBLE SUBGROUPS.

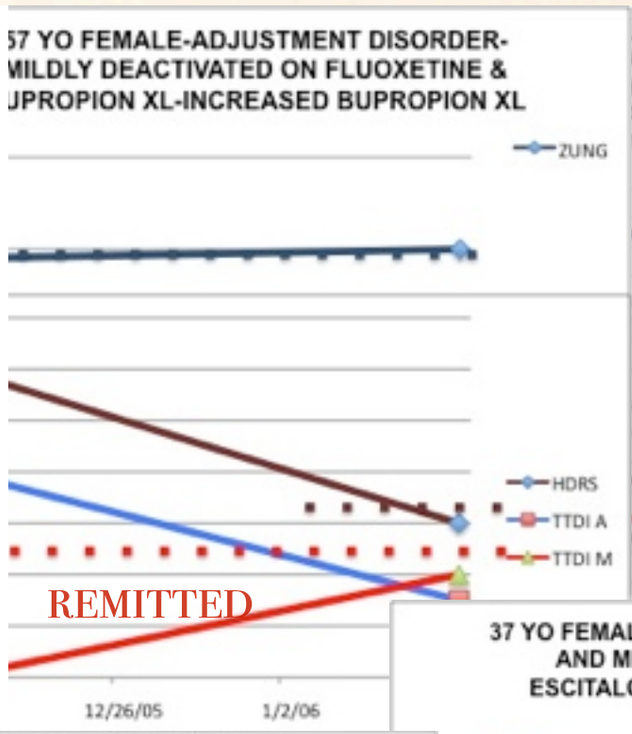
- THASE ME. THE FAILURE OF EVIDENCE-BASED MEDICINE TO GUIDE TREATMENT OF ANTIDEPRESSANT NONRESPONDERS. J CLIN PSYCHIATRY 2006; 67:1833-35

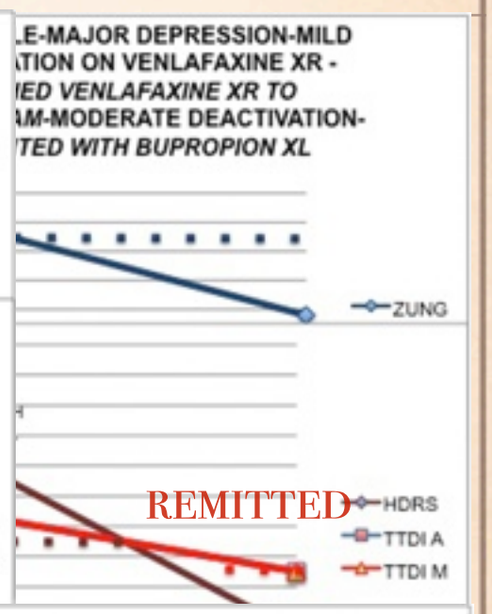
-KIERNAN M, KRAEMER HC, WINKLEBY MA, KING AC, TAYLOR CB: DO LOGISTIC REGRESSION AND SIGNAL DETECTION IDENTIFY DIFFERENT SUB-GROUPS AT RISK? IMPLICATIONS FOR THE DESIGN OF TAILORED INTERVENTIONS. PSYCHOL METHODS 2001; 6:35–48

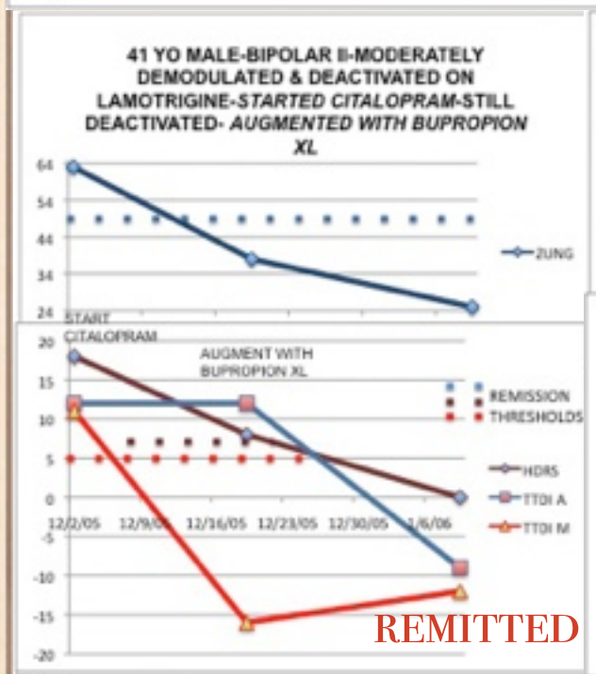
TTDI CASE ILLUSTRATIONS:

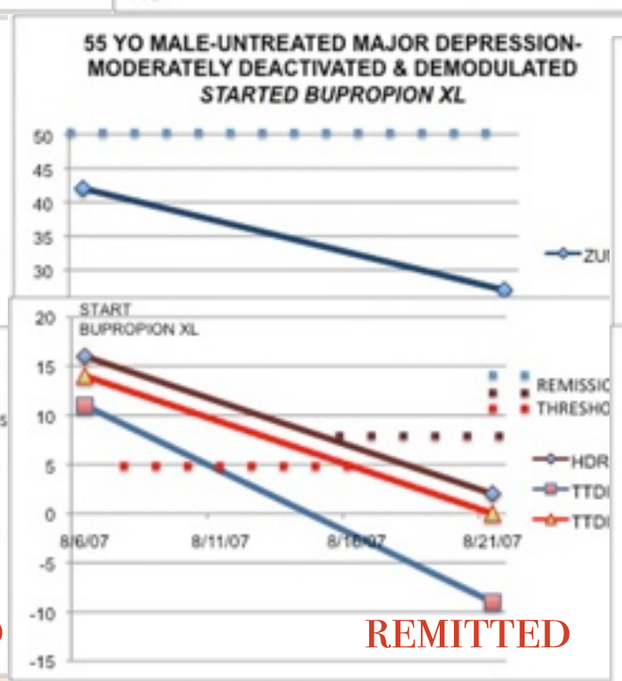


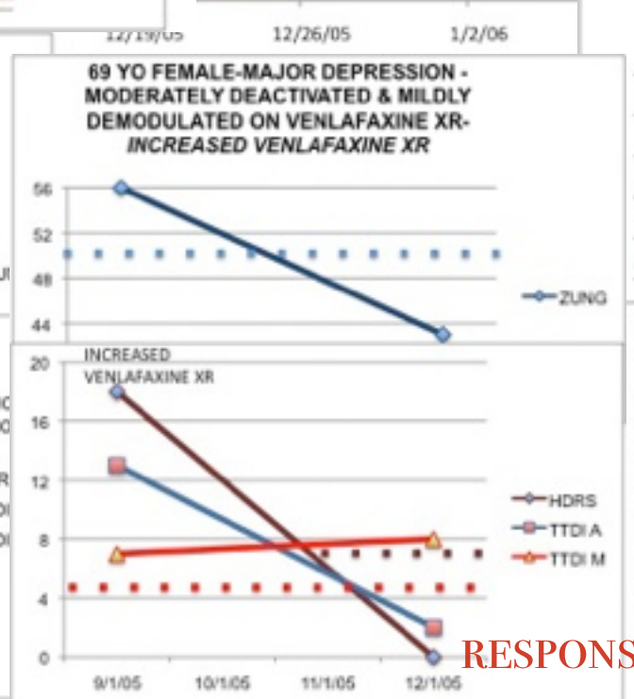


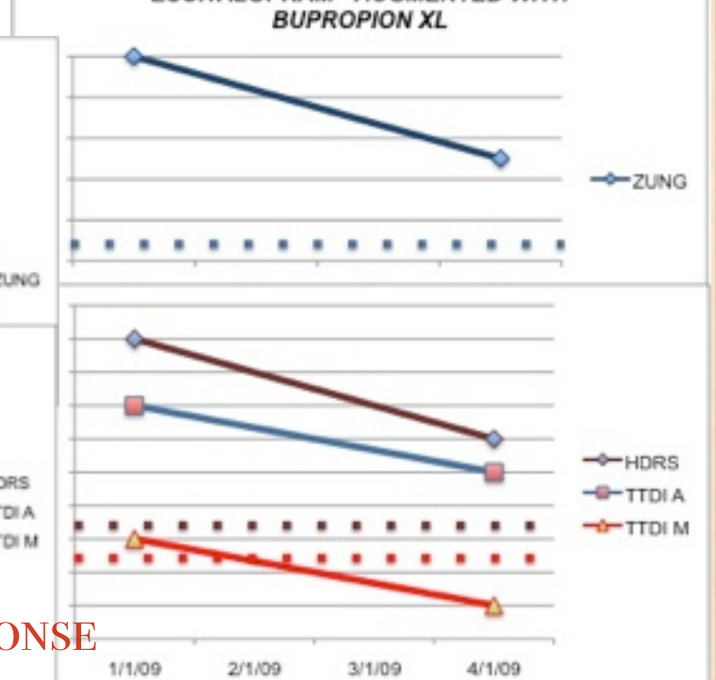












TTDI STUDY: LIMITS

NEED FOR:

- MORE FOLLOW-UP TTDI TESTING
- MORE HDRS AND ZUNG SDS CONCURRENT TESTING
- MORE OBSERVATION AND MONITORING OF CLINICIANS AND PATIENTS

ALGORITHMS: CONCLUSIONS

- INDIVIDUALIZED TREATMENT AS IMPLEMENTED WITH TESTS LIKE THE TTDI MAY IMPROVE ANTIDEPRESSANT REMISSION RATES

- MORE STUDIES USING TESTS LIKE THE TTDI ARE INDICATED

- INCLUDING DEMODULATED AND DEACTIVATED SUBTYPES IN DSM V MIGHT ENHANCE CLINICAL USEFULNESS