

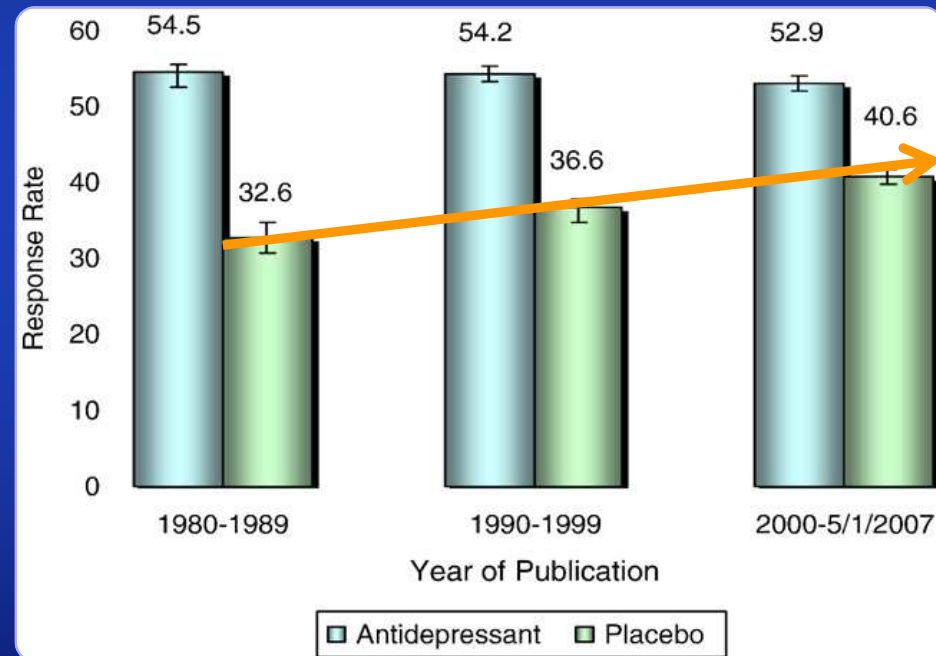
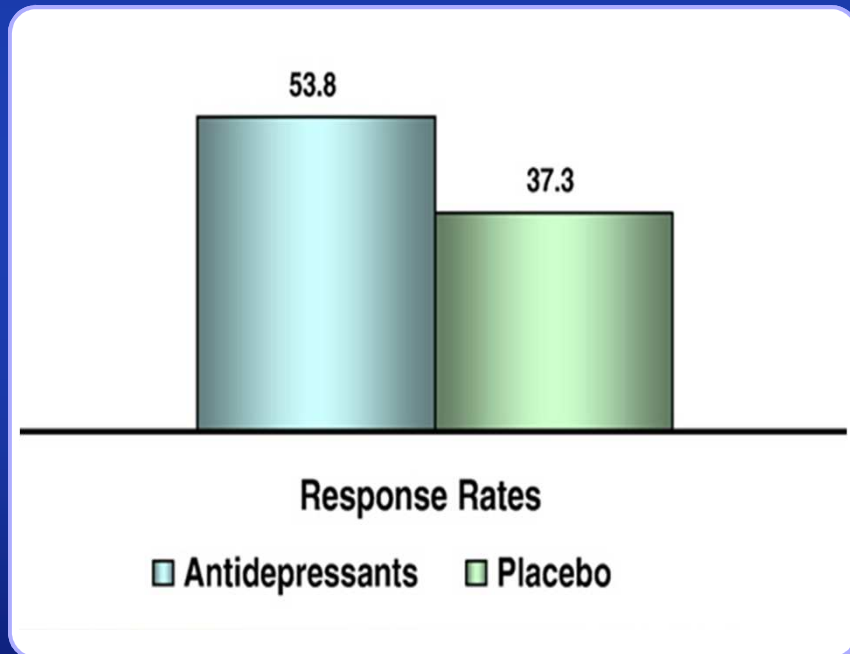
# Antidepressant treatment : are we ready for persona-lized treatments ?

... a clinician's view on precision medicine



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University Psychiatric Center, KU Leuven*

# 'Impersonalized' efficacy of antidepressants



# What is the first step towards PERSONA-lized medicine in depression ? Take the PERSON into account

- **Heterogeneity of tested populations**
  - What is major depression ?
- **Limitations of rating instruments**
  - Observer vs self-rating, past week or ESM, experimental settings ?
- **Patient and physician attitudes / beliefs : PERSONA**
- **Low adherence**

# DSM versus assessment tools : diversity in impersonalized depressive symptoms

## Observer-rating:

- HAMD : 17 (21,28)
- MADRS : 10
- **DSM** : **9**
- IDS : 30
- QIDS : 16

## Self-rating:

- HADS : 7
- MADRS-S : 9
- **PHQ** : **9**
- Zung (SDS) : 20
- Beck (BDI) : 21
- IDS-S : 30
- QIDS-S : 16
- Carroll (CDS) : 52 (61)
- CES-D : 20

# DSM versus assessment tools : Diversity in depressive symptoms

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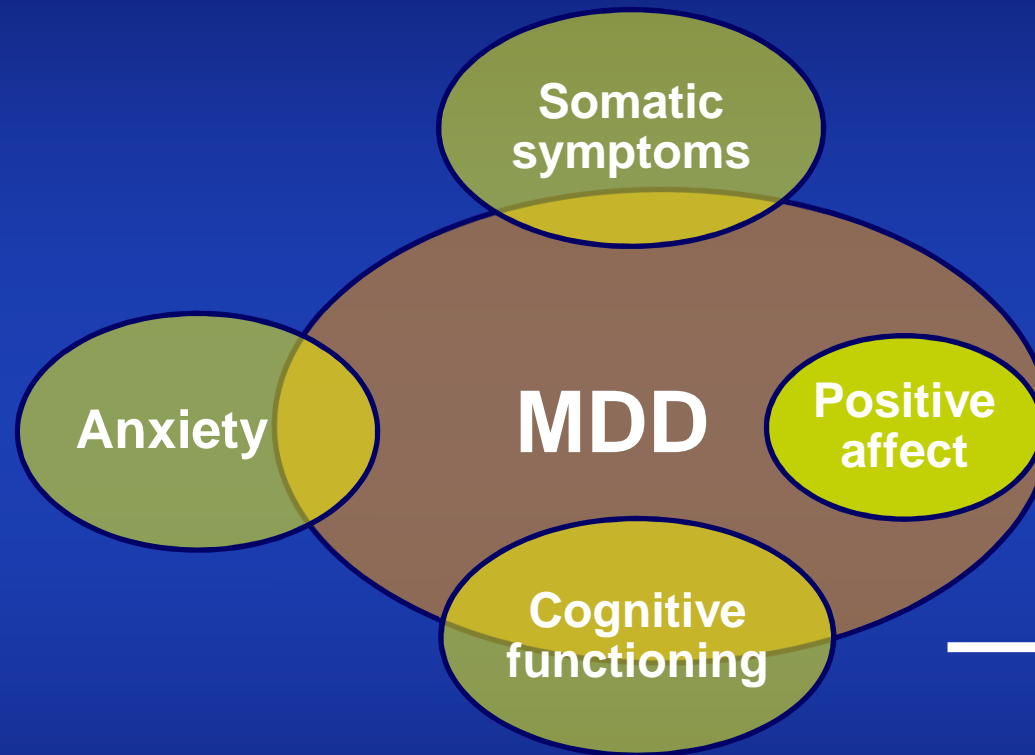
# Standard scales 'impersonalise'....

assessing change.....an art of lenses in a hall of mirrors ??



- **HAMD** : reflects change with TCAs
- **MADRS** : reflects change with a variety of ADs
  - The 10 items from the CPRS that changed most in antidepressant treatment
  - 'high sensitivity to change' : ???
- **BDI** : reflects change with CBT

# Heterogeneity of antidepressant marketing : towards personalized medicine ?



- \* **Functioning ?**
- \* Quality of life ?
- \* Meaningful life ?

if we cannot make a difference on the core symptoms,  
maybe we can make it on the associated symptoms

**RATING SCALES**  
**'IMPERSONALIZE' THE PATIENT**



# Is what we measure what matters for patients?

## Physicians top 10 ranking

Negative feelings : blue mood, despair, anxiety, depression
Feeling down, depressed or hopeless
Little interest or pleasure in doing things
Symptoms disrupted social life / leisure activities
Feeling tired or having little energy
How satisfied are you with yourself
How much are you enjoying life
Symptoms have disrupted your work
To what extent life is meaningful
How satisfied are you with your personal relationships

## Patients top 10 ranking

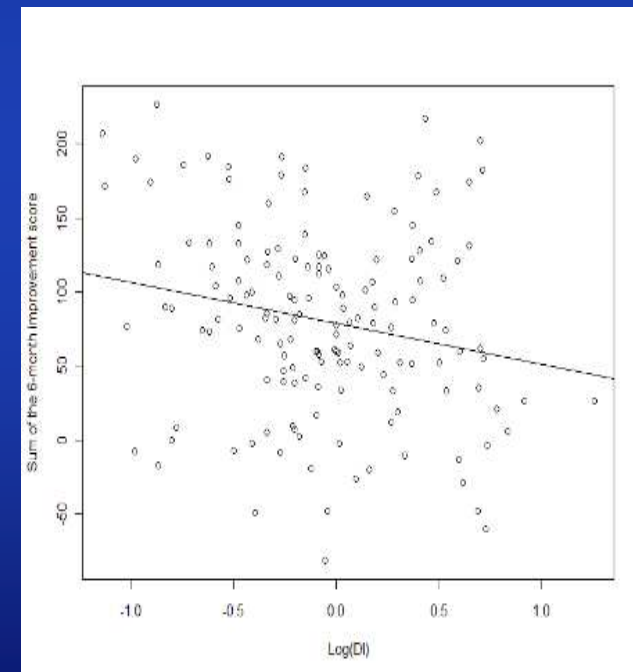
To what extent life is meaningful
How much do you enjoy life
How satisfied are you with yourself
How able are you to concentrate
Negative feelings : blue mood, despair, anxiety
Feeling tired or having little energy
Feeling down, depressed or hopeless
Feeling strong
How satisfied are you with your personal relationships
Feeling active

# Divergence in expectations between physician and patient influences 6 month outcome ( Multivariate - with baseline continuous divergence index )

- Combinaison of the psychometric scales

Effect	Est ± SE	P-value <sup>b</sup>
Intercept	104.0 ± 11.5	<.0001
Divergence	-22.4 ± 9.77	<b>0.024</b>

<sup>b</sup> GLMM model



**‘PERSONA’**

# PERSONA :

the power of belief, imagination, symbols, meaning, expectation, persuasion and self-relationship

- Hypericum Depression Trial Study group. Effect of hypericum perforatum in MDD: a randomized clinical trial
  - Hypericum versus sertraline versus placebo : **failed trial**

*(JAMA, 2002)*

# PERSONA :

the power of belief, imagination, symbols, meaning, expectation, persuasion and self-relationship

Treatment guessed by patient	Remission by guess group
sertraline	31% (P<.001 vs plc)
hypericum	37% (P<.001 vs plc)
placebo	22%

Treatment guessed by physician	Remission by guess group
sertraline	43% (P<.001 vs plc)
hypericum	33% (P<.001 vs plc)
placebo	6%

# PERSONA :

Patient's attitude towards medication and outcome (response rate)

Q-LES-Q item 15	Placebo	Antidepressant (escit, SNRI)
Rather negative attitude	34%	51%
Neutral attitude	36%	56%
Rather positive attitude	56%	69%

The difference between placebo and antidepressant is about as large as the difference between patients with a negative and a positive attitude to medication

# PERSONA

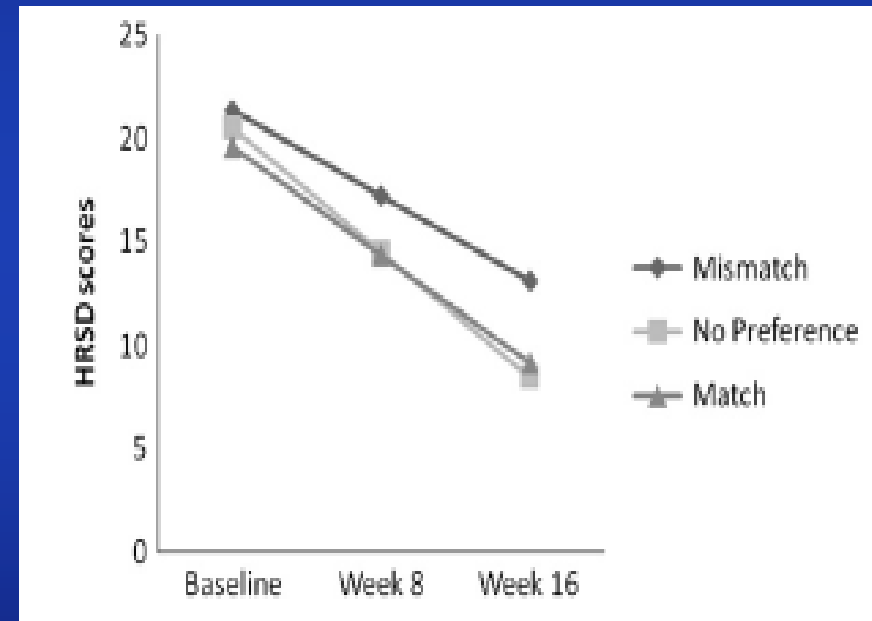
## Psychosocial and clinical factors predicting outcome : ceiling effect ?

- **Factors predicting remission after 6 months of treatment :**
  - Being married / living together OR: 2.81
  - Age OR: 0.86
  - Baseline pain severity OR: 0.86
  - Number of previous depressive episodes OR: 0.74
  - Unemployment OR: 0.27

# PERSONA :

## Patient preference and outcome

- 48% prefer psychotherapy
- 18% prefer antidepressants
- 34% no preference







# ADHERENCE

The most expensive drug is the one that has not been taken...

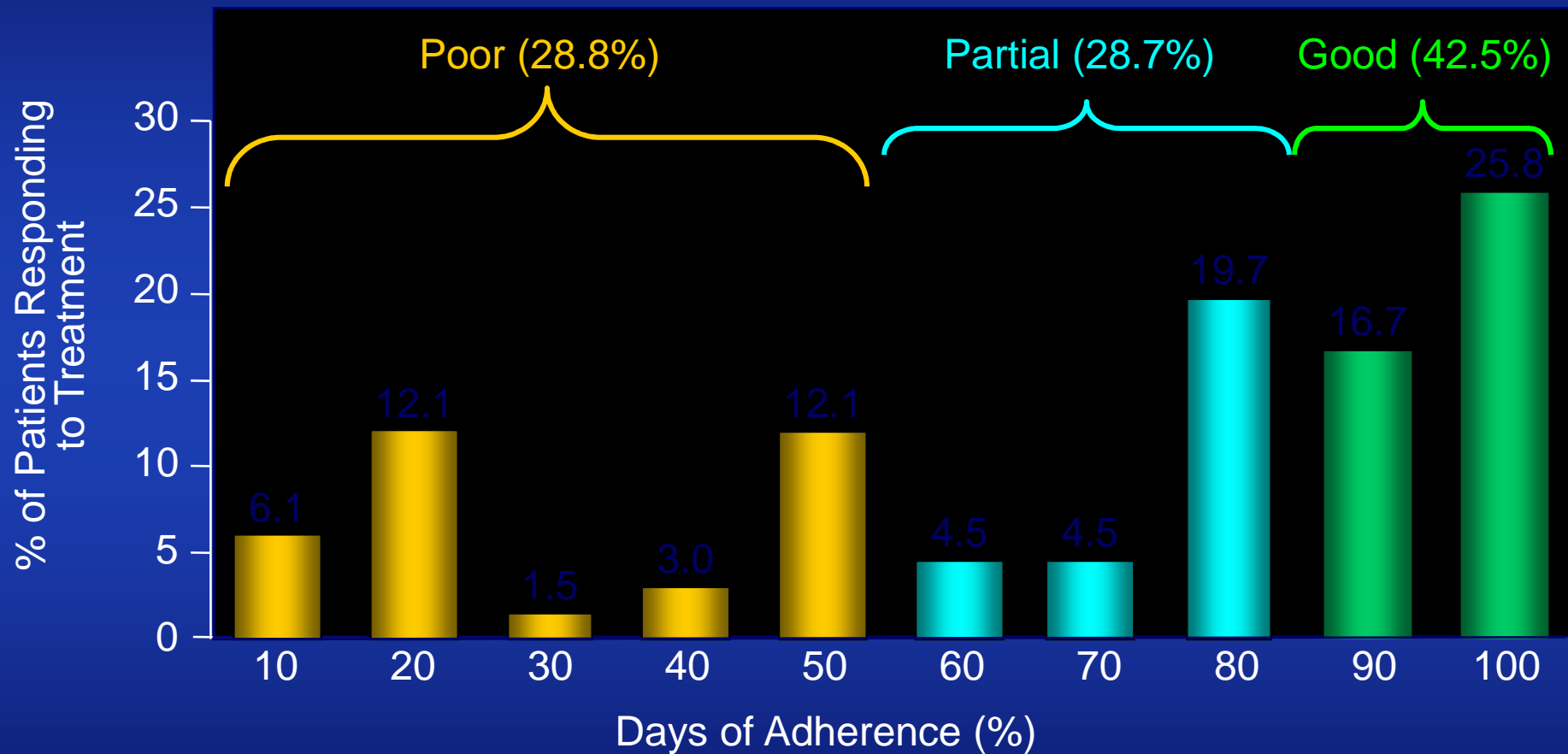
# *MEMIS*<sup>®</sup>

*Medication Management System*

The Total-System Solution for  
a Leading Cause of Medication Failure



# Patient Adherence : Frequency Distribution





**TAKING INTO ACCOUNT  
THE PERSONA (OR ANIMA ?)  
IS THE FIRST STEP  
TO PERSONA-LIZED TREATMENT  
OF DEPRESSION**

# Early abuse (4-7 years) predicts a worse outcome

## *Abuse/interpersonal violation*

- Were you physically abused?
- Were you sexually abused?
- Were you emotionally abused?
- Did you experience extreme poverty or neglect?
- Did you witness domestic violence within your family?
- Did you experience sustained bullying or rejection by schoolmates?

## *Family breakup*

- Did your parents divorce or separate?
- Were you separated for a long period from a parent, brother or sister?
- Was there sustained conflict within your family?

## *Family health/death*

- Did one of your parents, a brother or sister die?
- Did one of your parents, a brother or sister experience a life-threatening illness?

## *Personal health*

- Did you undergo major surgery or repeated hospitalization?
- Did you experience a life-threatening illness or injury?

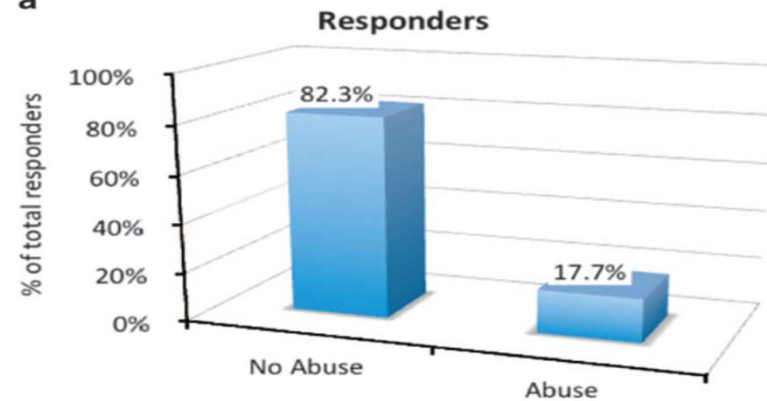
## *Disaster/war*

- Did you witness first-hand a natural disaster such as earthquake, flood or fire?
- Did you witness warfare?

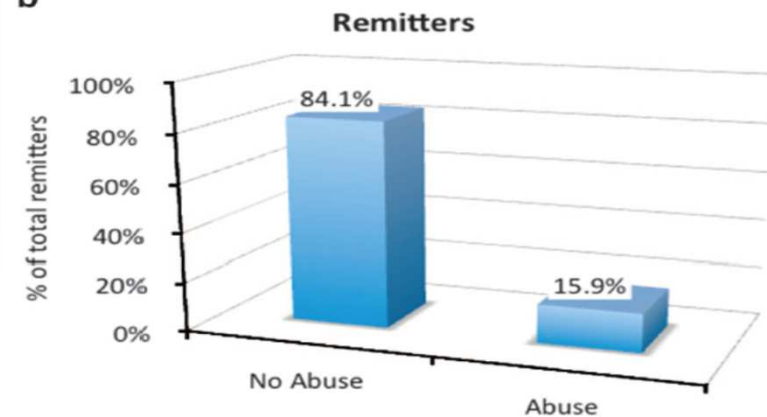
## *Other traumatic events*

- Were you born prematurely, or experience other birth complications?
- Were you adopted?
- Was your house destroyed by fire or other means?

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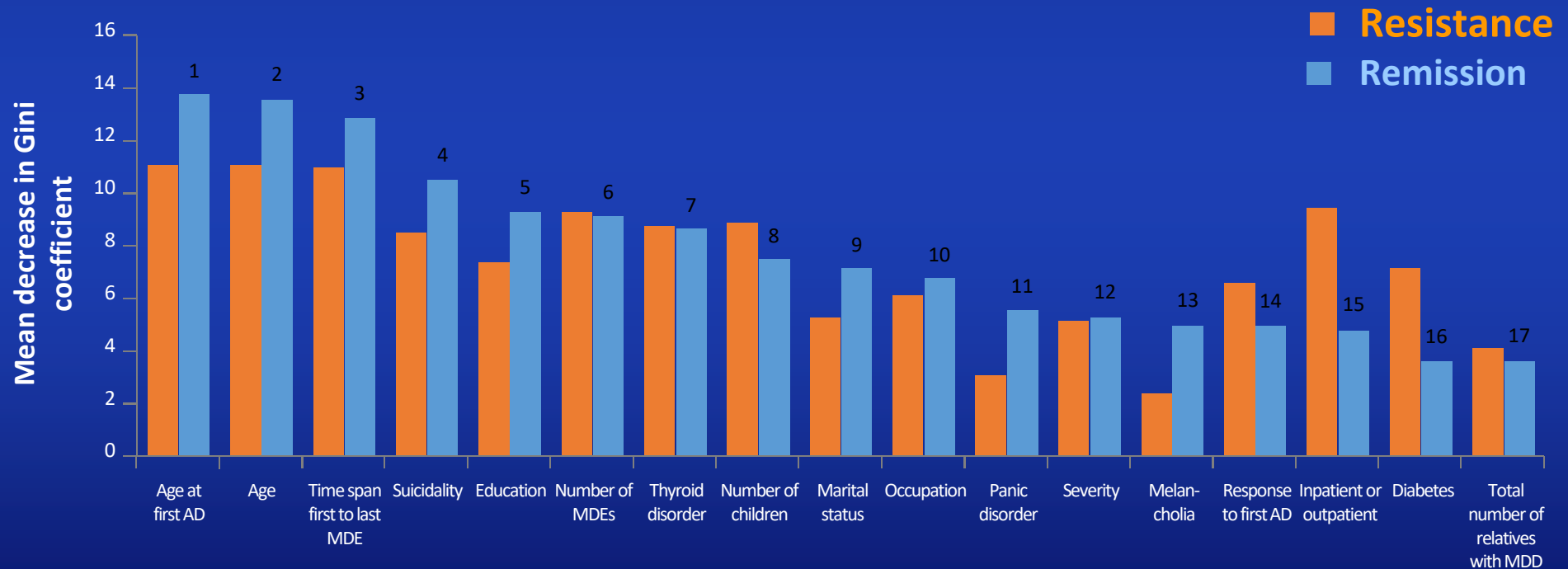


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# Personalized outcome prediction : feasibility ? outcome predictors with machine learning

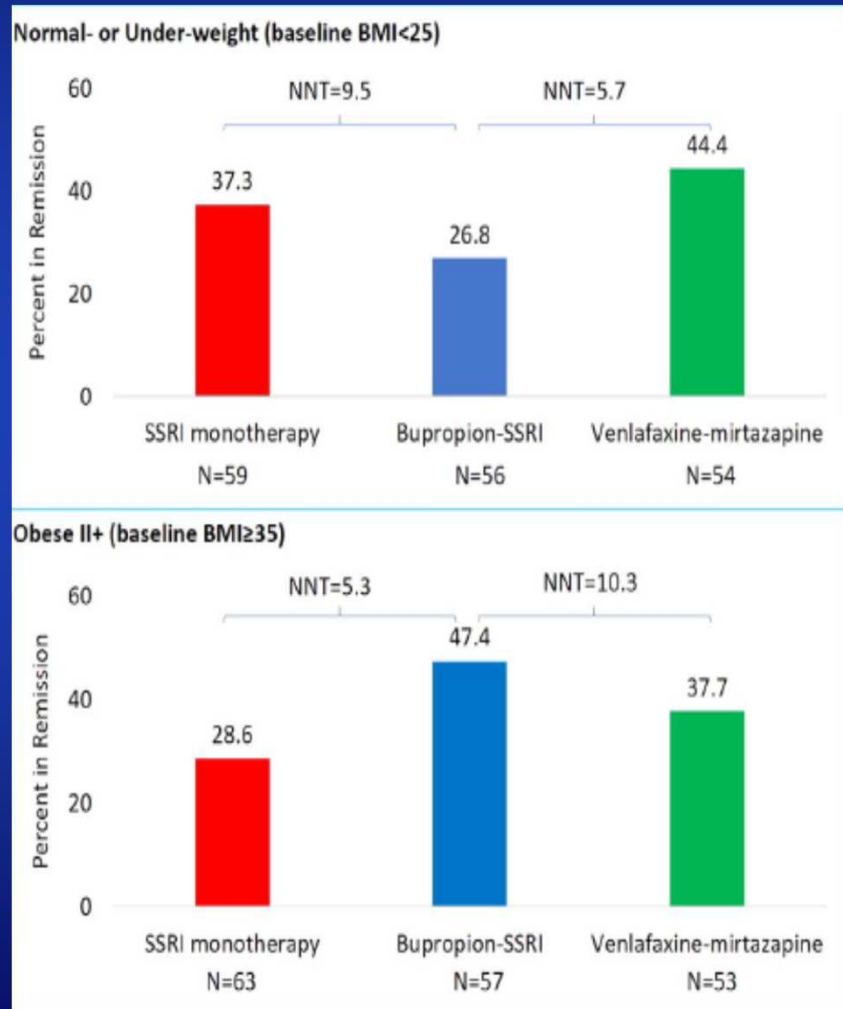
77.7% of predictions for remission correct  
65.5% of predictions for TRD correct



Data from TRD I, II and III: 2000 – 2015 (n = 480; full data set)

Kautzky A, et al. *J Clin Psychiatry*. 2017;78:215-22.

# BMI and choice of antidepressant ??



## In morbid obesity (II):

- Bupropion better than
  - SSRI
  - Venlafaxine-mirtazapine

## In overweight or obesity (I):

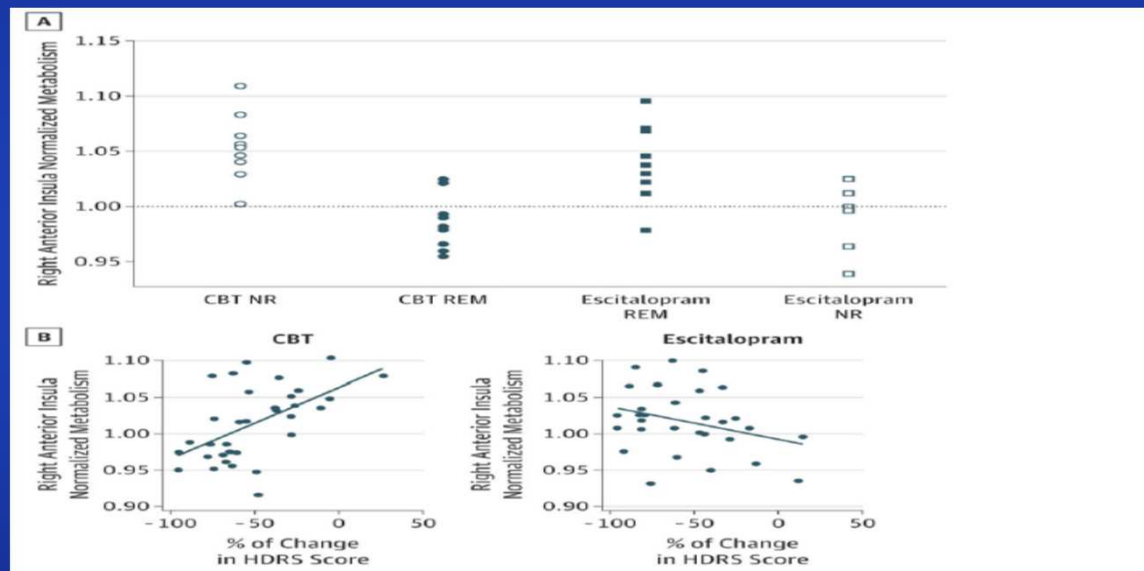
\* no difference

## In normal- or under-weight:

- \* venla-mirtazapine better than bupropion-SSRIs
- \* SSRI better than bupropion-SSRI

# Right anterior insula normalized metabolism\* differentially predicts outcome with CBT or with escitalopram

\* relative to whole-brain metabolism



Right insula hypometabolism predicts higher remission rates with CBT

Right insula hypermetabolism predicts higher remission rates with escitalopram



# CRP and depression (symptom severity)

- **Higher CRP associated with higher depression severity**
  - but mainly in women
- **Observed mood, cognitive symptoms, interest-activity (and borderline significant for suicidality) show strongest association with CRP**
  - but only in women
- **Overall: higher CRP weakly associated with poor outcome**

# CRP differentially predicts outcome with escitalopram or nortriptyline

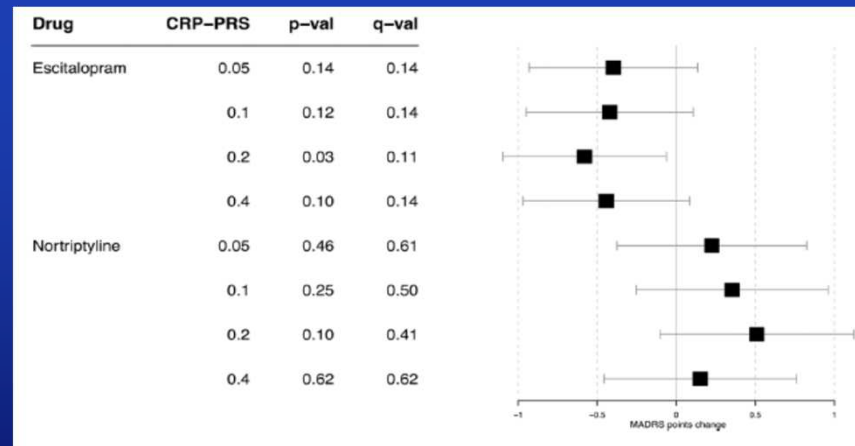
- **GENDEP :**
  - Overall efficacy: escitalopram (N=115) = nortriptyline (N = 126)
- CRP and its interaction with drug explains more than 10% of the individual-level variance in treatment outcome:
  - <1mg/L (low cv risk and low systemic inflammation) :
    - Escitalopram significantly better than nortriptyline
  - >3mg/L (high cv risk and high systemic inflammation) :
    - Nortriptyline significantly better than escitalopram

# Were these serum CRP findings 'state' dependent ? Opposite findings for Polygenic Risk Score (PRS) (genotyping 550.337 SNPs)

CRP is for about 50% heritable :

PRS is the individual's genetic liability to systemic inflammation

Higher CRP-PRS associated with slightly better outcome on escitalopram  
Lower CRP-PRS associated with better outcome on nortriptyline



CRP-PRS explains about 5% of the variance in outcome