



# Mood disorders

## \* Depression \*

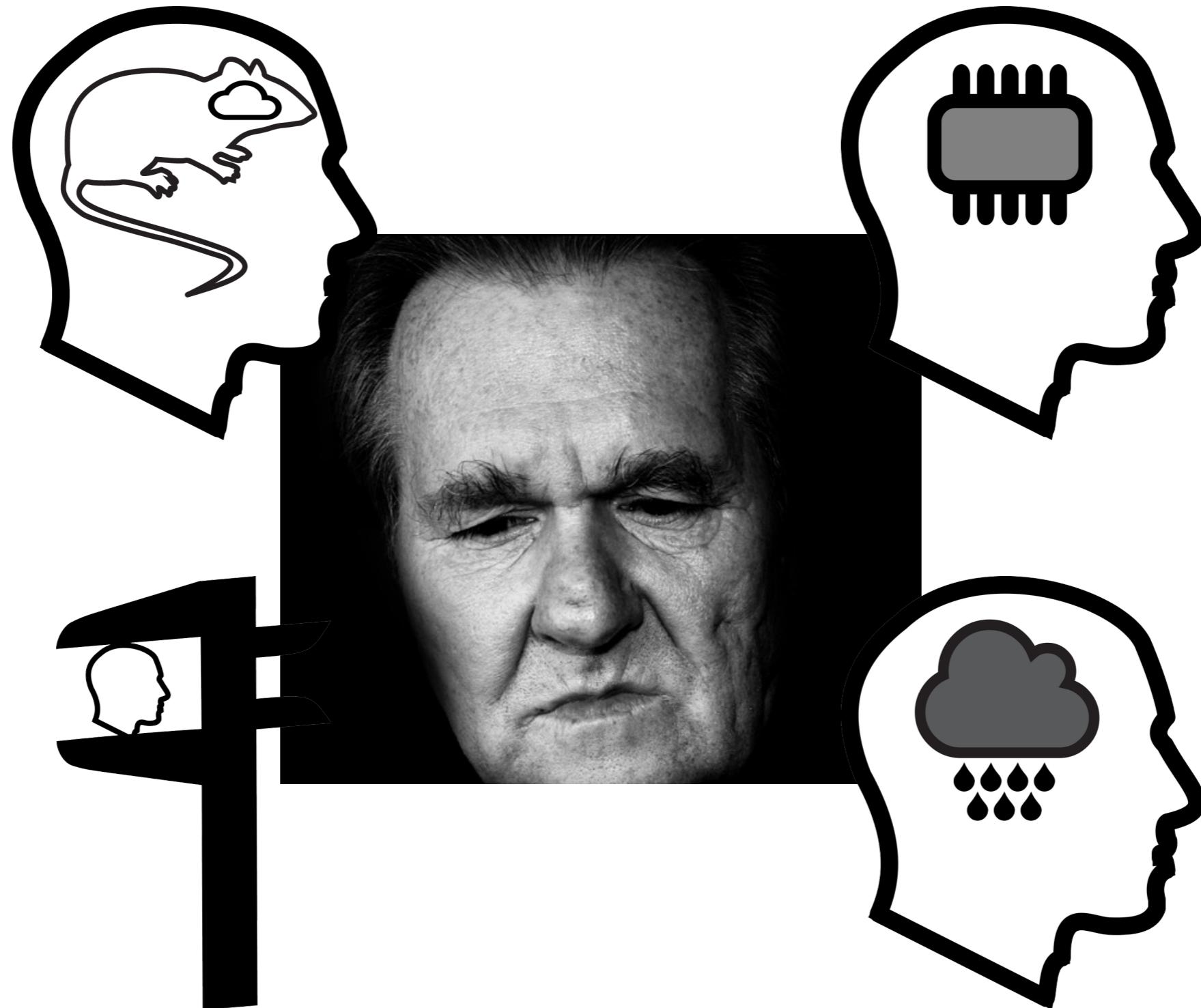
Dominik R Bach

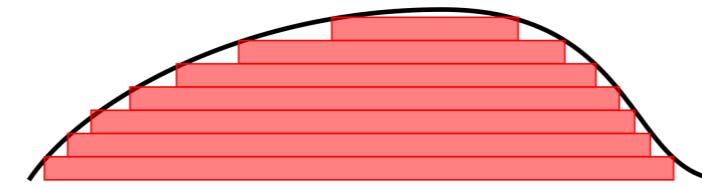
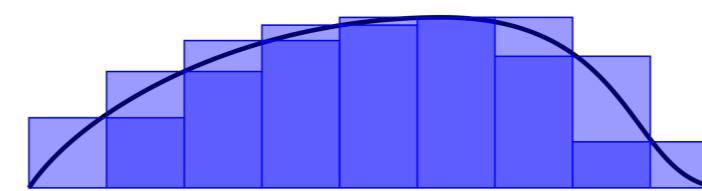
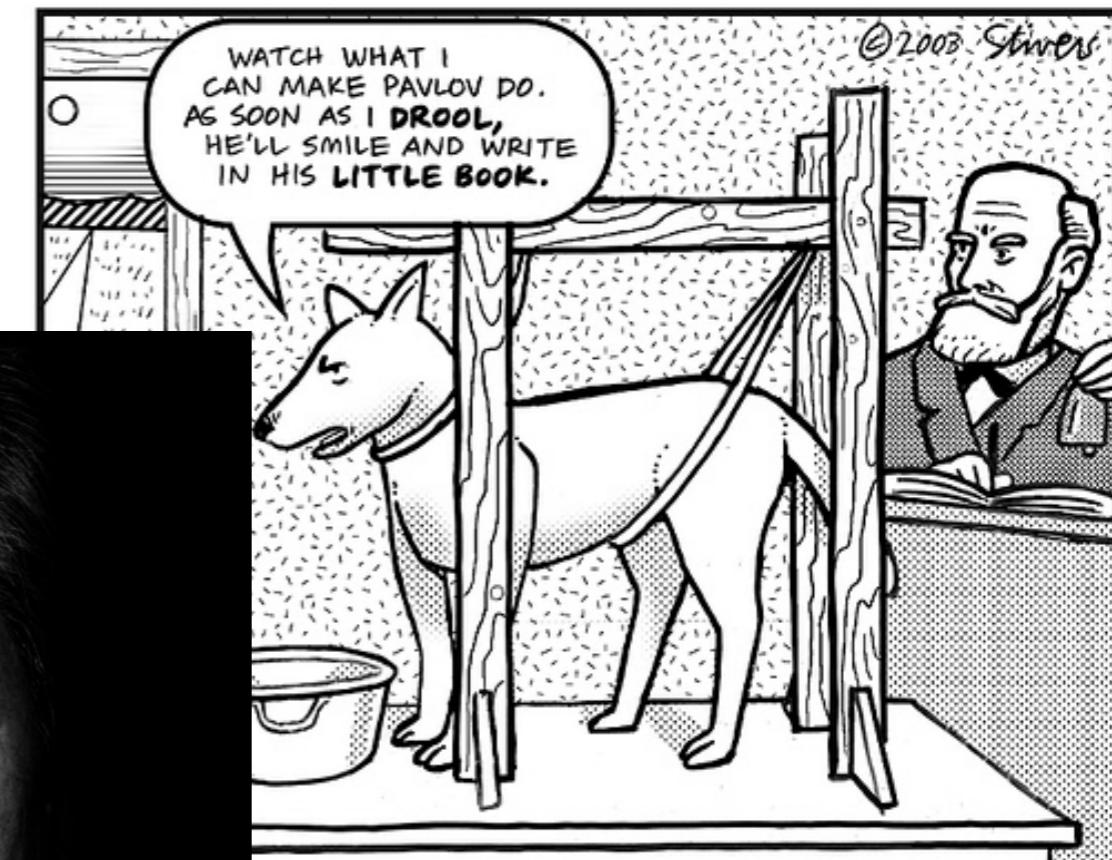
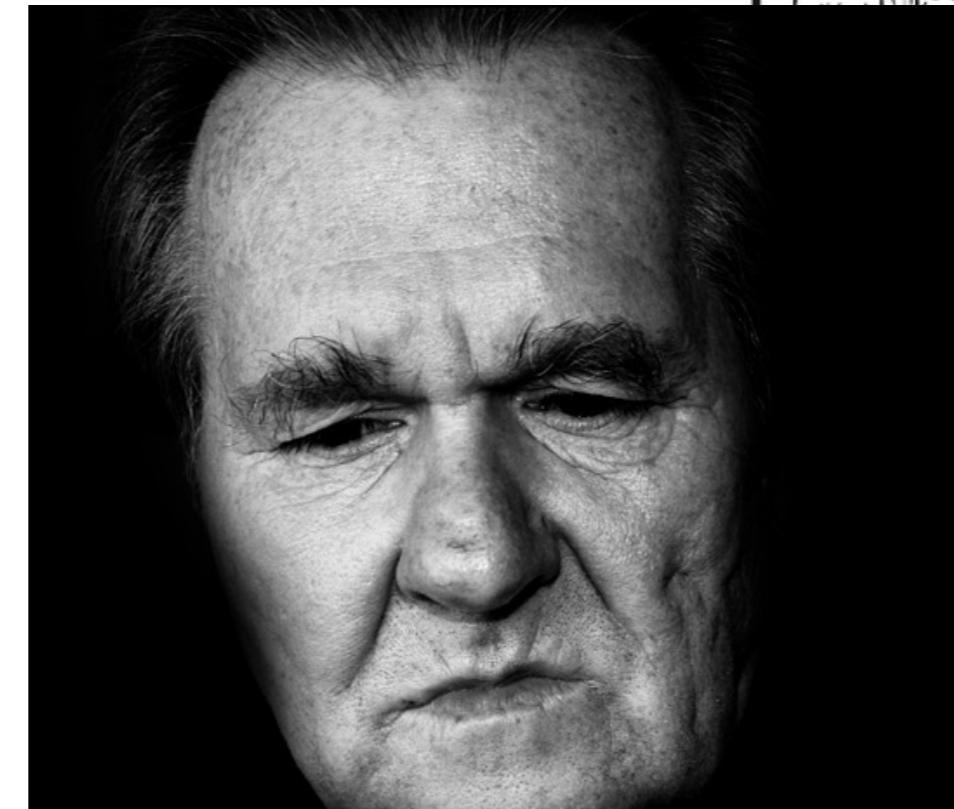
*Division of Clinical Psychiatry Research  
University of Zurich*

29.08.2016

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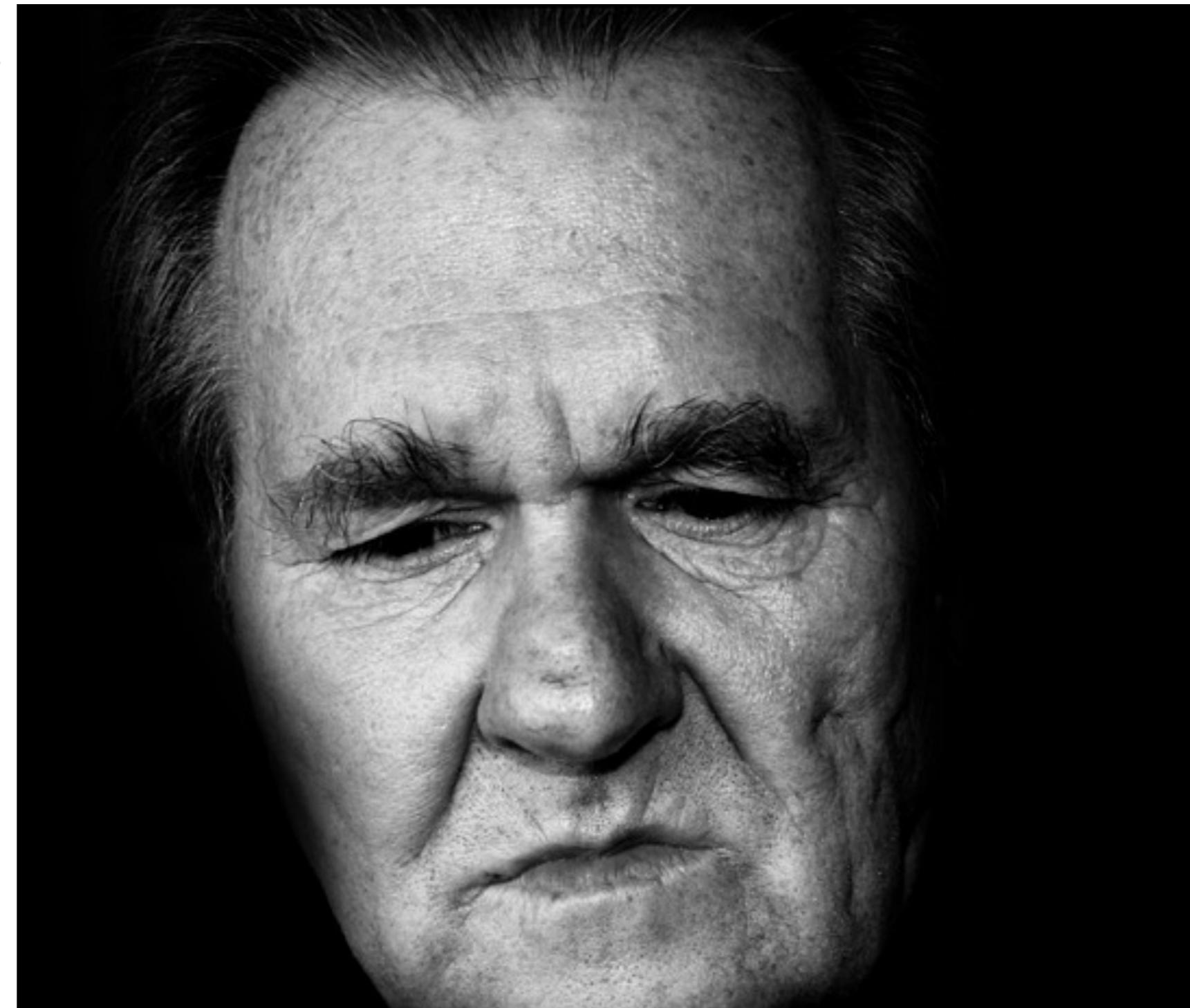




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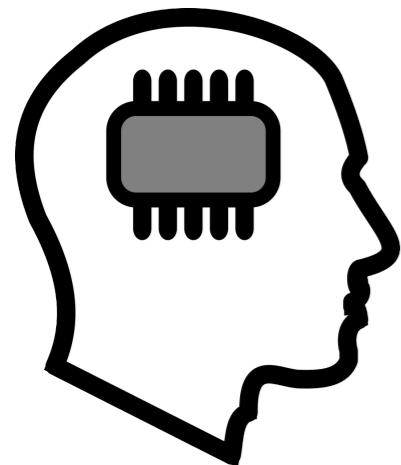
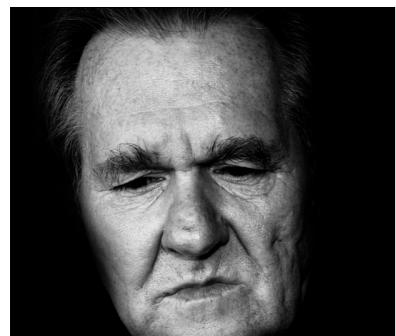
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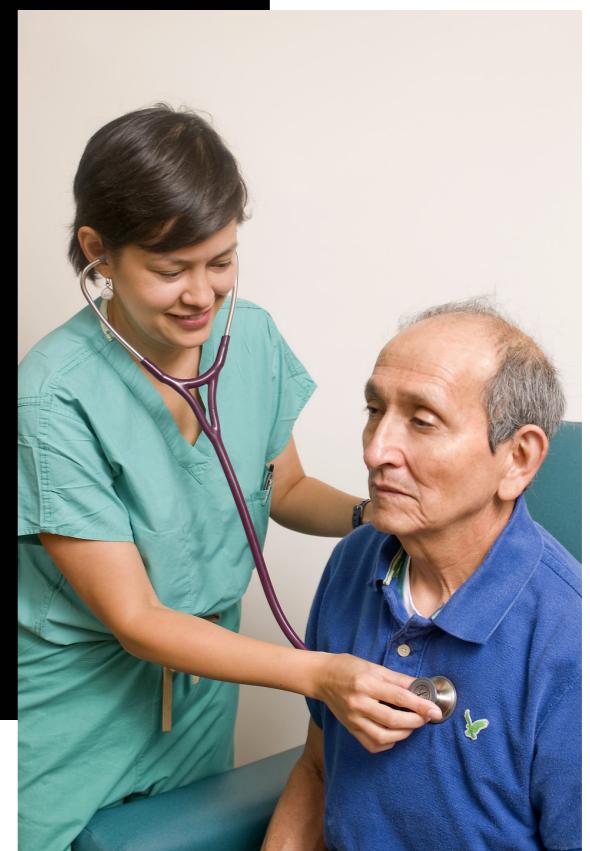
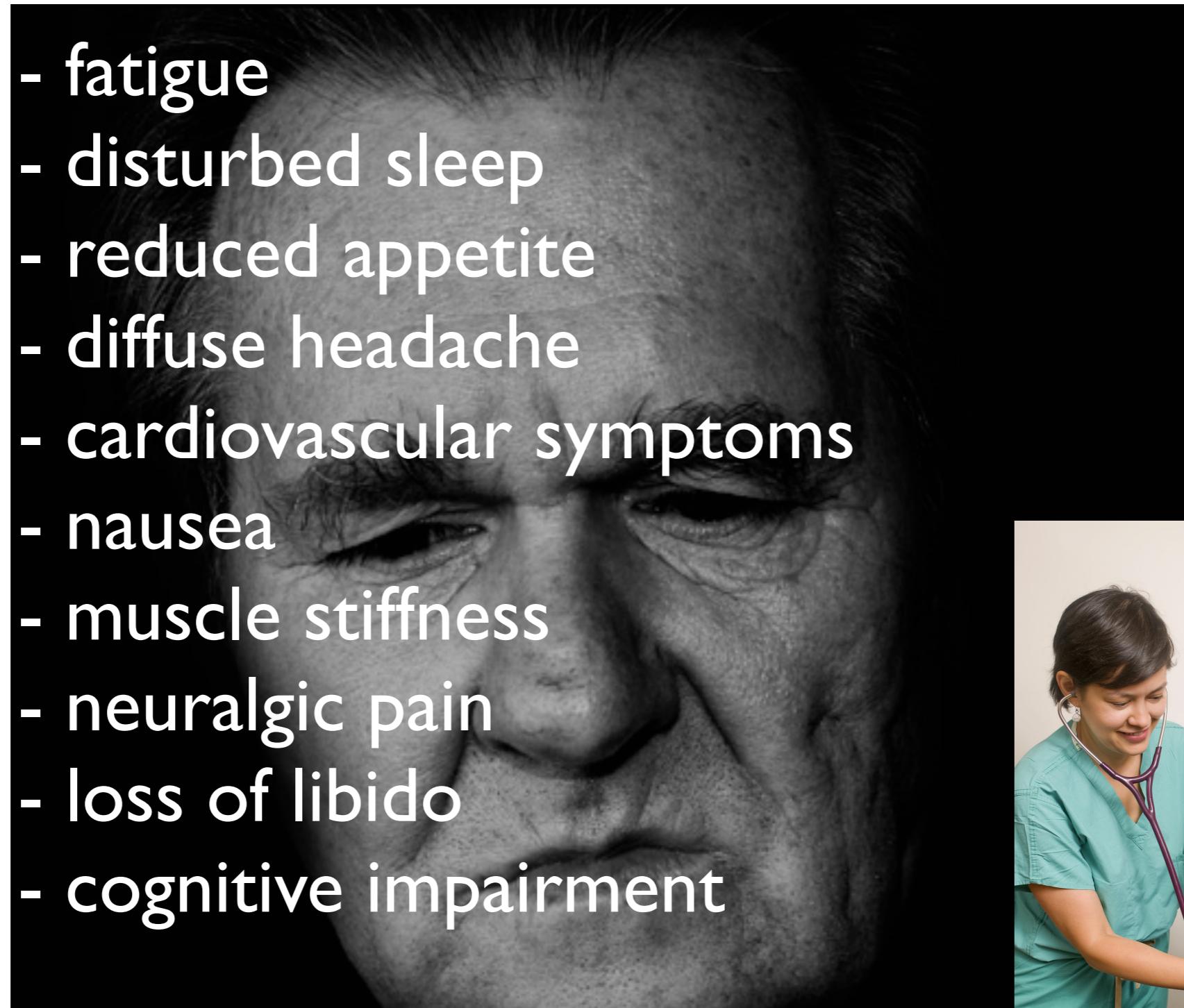
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# Clinician's wish list



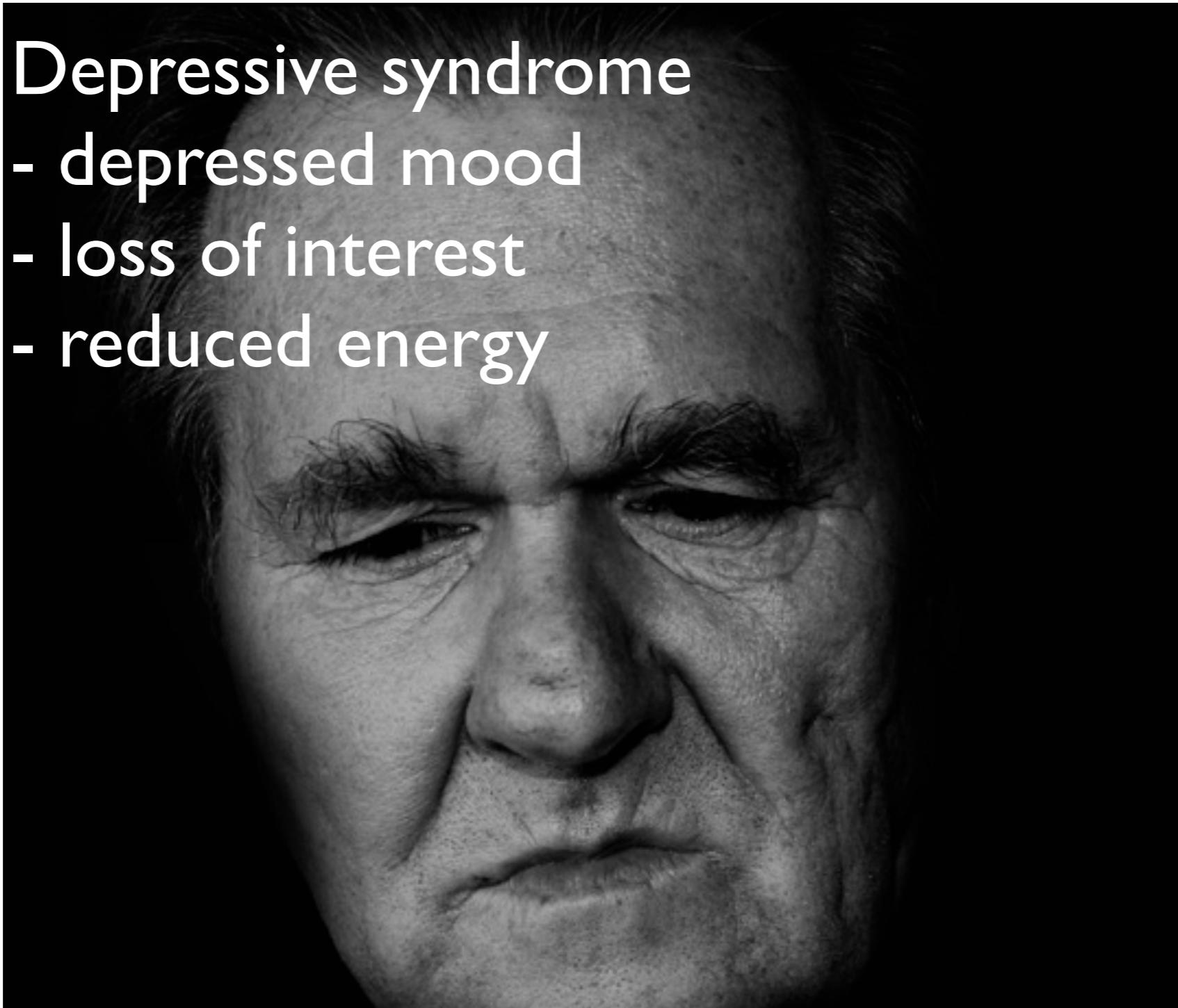
# Primary symptoms

- fatigue
- disturbed sleep
- reduced appetite
- diffuse headache
- cardiovascular symptoms
- nausea
- muscle stiffness
- neuralgic pain
- loss of libido
- cognitive impairment



## Depressive syndrome

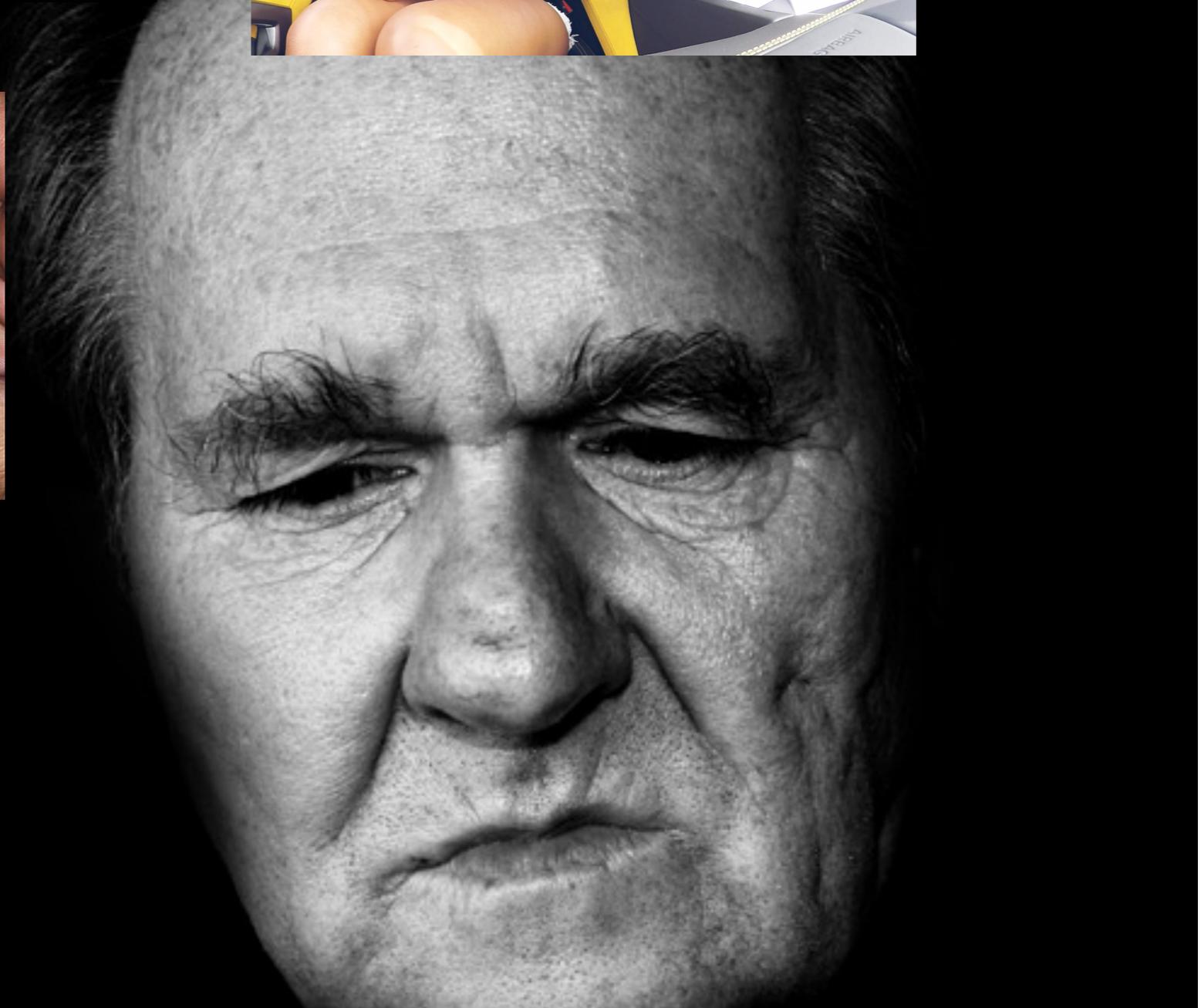
- depressed mood
- loss of interest
- reduced energy





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# Differential diagnosis

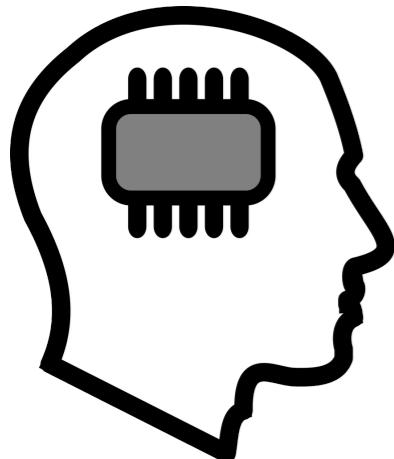
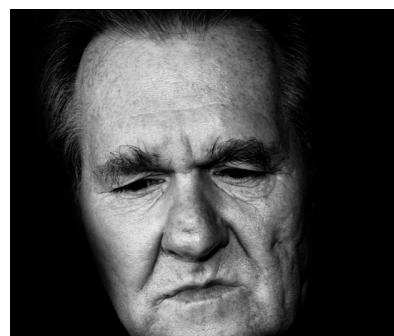
## - bipolar I depression

~5% first-episode depression: 60% of BD are diagnosed as UD on first episode, Cardoso de Almeida 2013

- depression caused by drug dependence
- amotivational syndrome due to cannabis use (even recreational)
- schizophrenic prodromi, schizophrenia simplex
- mood swing in BPD

## Differential diagnosis

- establishing the evidence takes time (up to weeks)
- prior knowledge: age, gender, symptom dynamics, profile of additional symptoms
- doctors are fantastic model inversion machines for sparse data but individually they don't see that many patients
- to beat a trained and interested doctor, you need BIG data (100s of data points per patient, or 10'000s of patients)

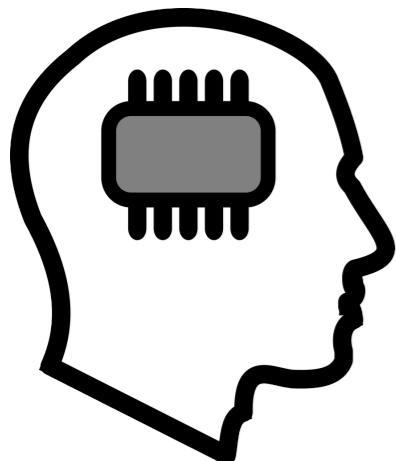
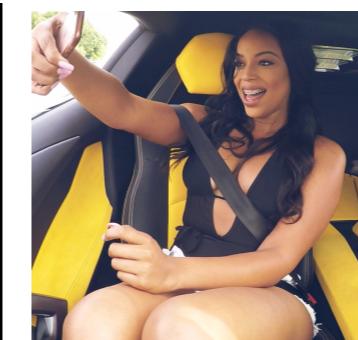
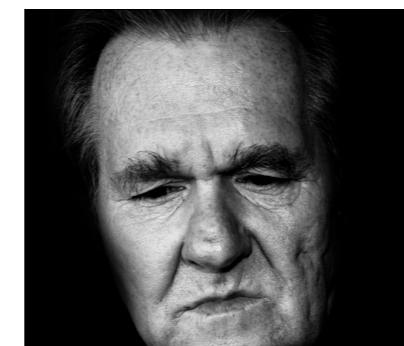
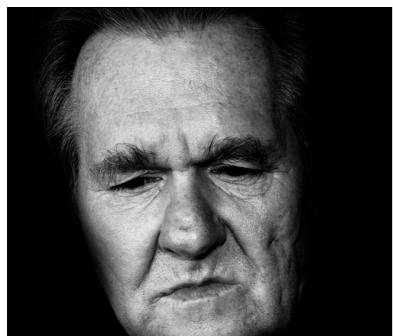


## Tests for differential diagnosis



Reification  
Comorbidity





Tests for differential diagnosis  
Tests for uni- vs. bipolar

## Major symptoms

- depressed mood
- loss of interest
- reduced energy

## Minor symptoms

- reduced concentration/attention
- reduced self-esteem
- ideas of guilt
- pessimism
- suicidal thoughts
- disturbed sleep
- diminished appetite

## Other symptoms

- anxiety
- motor restlessness or motor slowing
- morning low
- decreased libido



## Major symptoms

- depressed mood
- loss of interest
- reduced energy

Major symptoms must be present most of the day, every day, > 2 weeks

Mild episode:

2 major + 3 minor over

## Minor symptoms

- reduced concentration/attention
- reduced self-esteem
- ideas of guilt
- pessimism
- suicidal thoughts
- disturbed sleep
- diminished appetite

Moderate episode:  
3 major + 3-4 minor

Severe episode:

3 major + 4 minor  
some must be pronounced

## Other symptoms

- anxiety
- motor restlessness or motor slowing
- morning low
- decreased libido

Psychotic symptoms  
(hallucinations, delusions)

## Major symptoms

- depressed mood
- loss of interest

## Minor symptoms

- reduced energy
- reduced concentration/attention
- reduced self-esteem/  
ideas of guilt
- suicidal thoughts
- disturbed/increased sleep
- diminished/increased appetite
- motor restlessness or motor slowing



## Major symptoms

- depressed mood
- loss of interest

All symptoms must be present most of the day, every day, > 2 weeks  
1 major + overall 5

## Minor symptoms

- reduced energy
- reduced concentration/attention
- reduced self-esteem/  
ideas of guilt
- suicidal thoughts
- disturbed/increased sleep
- diminished/increased appetite

Severity rated clinically  
Psychotic symptoms  
(hallucinations, delusions)

- motor restlessness or motor slowing

Image: A black and white close-up photograph of a man's face, showing him with his eyes closed and a somber expression, resting his chin on his hand.

**Table 2**

Meta-analytic estimates for primary outcomes and for subgroup analyses.

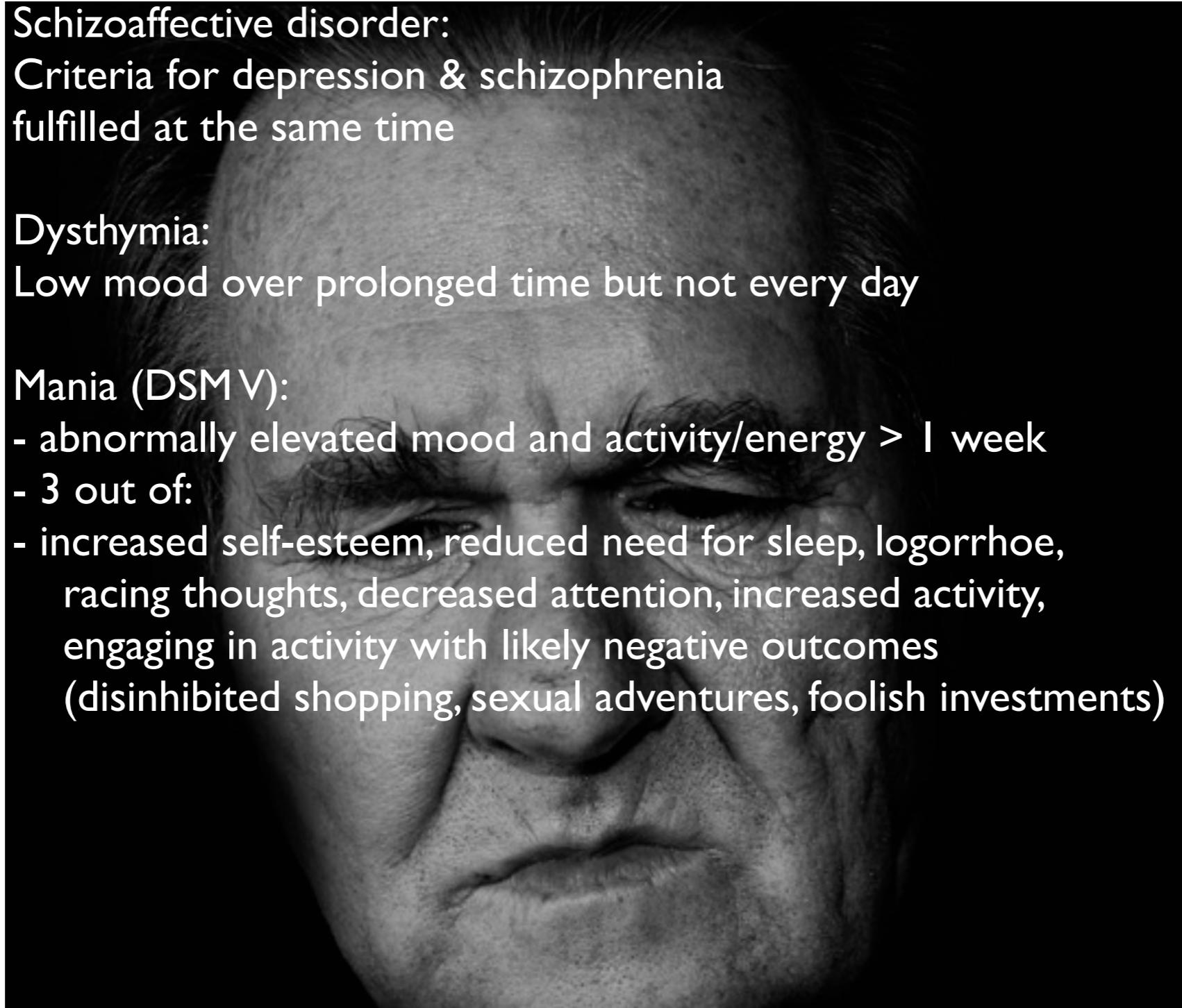
Reliability by disorder		Schizoaffective disorder (SAD)					Schizophrenia (SCH)					Bipolar disorder (BPD)					Unipolar depression (DEP)				
		n	k	SE	I <sup>2</sup>	p	n	k	SE	I <sup>2</sup>	p	n	k	SE	I <sup>2</sup>	p	n	k	SE	I <sup>2</sup>	p
All studies		25	0.57	0.08	98	/	23	0.80	0.02	70	/	17	0.82	0.02	38	/	23	0.75	0.03	82	/
Diagnostic interview	Consistent use	16	0.56	0.12	97	0.830	14	0.79	0.05	78	0.643	12	0.83	0.04	30	0.454	15	0.78	0.04	76	0.121
	Inconsistent use	9	0.58	0.04	63		9	0.81	0.02	47		5	0.80	0.03	50		8	0.70	0.04	82	
Diagnostic manual	DSM-III-R, -IV, -5	11	0.59	0.09	85	0.902	10	0.79	0.06	74	0.998	9	0.81	0.05	47	0.511	9	0.77	0.06	84	0.047
	ICD-10	9	0.55	0.05	81		9	0.79	0.03	73		7	0.79	0.03	61		7	0.67	0.04	85	
	RDC	6	0.60	0.13	88		5	0.79	0.05	23		3	0.88	0.07	0		6	0.82	0.05	49	
Kind of kappa	Cohen's kappa	9	0.51	0.08	73	0.729	7	0.77	0.06	45	0.482	6	0.84	0.05	0	0.705	8	0.72	0.07	82	0.170
	Fleiss' kappa	5	0.57	0.02	3		5	0.83	0.02	66		4	0.79	0.03	64		4	0.67	0.04	89	
	Calculated kappa	4	0.51	0.30	98		4	0.74	0.13	92		2	0.82	0.14	72		4	0.81	0.06	68	

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# Related diagnoses



Schizoaffective disorder:  
Criteria for depression & schizophrenia  
fulfilled at the same time

Dysthymia:  
Low mood over prolonged time but not every day

Mania (DSM V):

- abnormally elevated mood and activity/energy > 1 week
- 3 out of:
- increased self-esteem, reduced need for sleep, logorrhoe,  
racing thoughts, decreased attention, increased activity,  
engaging in activity with likely negative outcomes  
(disinhibited shopping, sexual adventures, foolish investments)

12-month prevalence	Men	Women	Seniors in institutions
<i>Major unipolar episode</i>	5%	10%	15-25%
<i>Bipolar disorder</i>	BP I: 0.5-1% BP II: 0.5-1%		
<b>Onset</b>	50% have onset before 30 yrs		

# Comorbidity

>= 1 comorbid psychiatric diagnosis	60% of UD	
3 comorbid psychiatric diagnoses	25% of UD	
Anxiety and panic disorders	50% life time comorbidity	
Dependence disorder	33% life time comorbidity	
Increased risk for non-psychiatric diagnosis	1.8 fold 12 months after remission	cardiovascular, cerebrovascular, stroke, dementia

< 50% symptom reduction	no/minimal effect
> 50% symptom reduction	response/part remission
100% symptom reduction or symptoms below cut-off	remission
New episode within 6 months	relapse
New episode after more than 6 months	recurrence

NICE	DGPPN
Mild to moderate depression, initial	Low intensity psychosocial intervention
Mild to moderate depression, persistent	Drug AND/OR psychotherapy
Moderate to severe depression	Drug AND psychotherapy
Very severe depression or risk to life	Drug AND psychotherapy, in-patient care
	Mild depression, initial
	Mild depression, persistent
	Moderate depression
	Severe depression
	Low intensity psychosocial intervention
	Psychotherapy
	Drug OR psychotherapy
	Drug AND psychotherapy

Cognitive/behavioural therapy (CBT), Psychodynamic psychotherapy, Psychoanalysis, Systemic psychotherapy, Interpersonal Psychotherapy (IPT), Person-centred psychotherapy  
severe depression: CBT, IPT

NICE guidelines, DGPPN guidelines



**Group 1: SSRI**  
(similar: Trazodon)

**Group 2: SNRI**  
(Venlafaxin, Duloxetin)

**Group 3: Tricyclic  
antidepressants**

**Group 4: alpha2-  
antagonists (Mirtazapin,  
Mianserin)**

**Group 5: Lithium**

**Group 6:  
Antipsychotics**  
(Aripiprazol, Risperidon,  
Quetiapin, Olanzapin)

**Group 7: MAO-  
Inhibitors, Bupropion,  
Agomelatin and others**



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# Treatment resistance

(30-50% of patients)

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Group 1-3 + 4  
Mirtazapin

Group 1-4 + 5 Lithium

Group 1-4 + 6 Atypical  
antipsychotics  
[Group 1-4 + T3 (?)]

**Group 5: Lithium**

**Group 6:  
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Electroconvulsive therapy (ECT): 60-90% remission rate in treatment-resistant depression

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# Treatment resistance

(30-50% of patients)

Group  
(similar)

Sample size?

**CONSENSUS (N=250), SOLVD  
(N=2500 patients), SAVE (N=2500  
patients) HOPE (N=10'000 patients)**

Group  
(Venlafaxine)

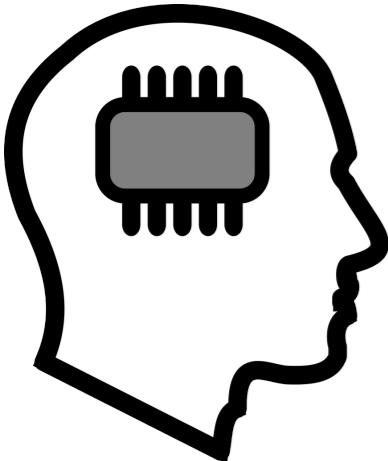
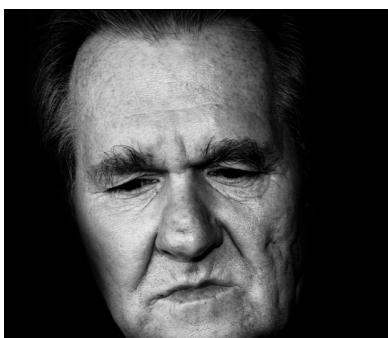
Direct comparison?

**ALLHAT (N=42'000, 4 drugs)**

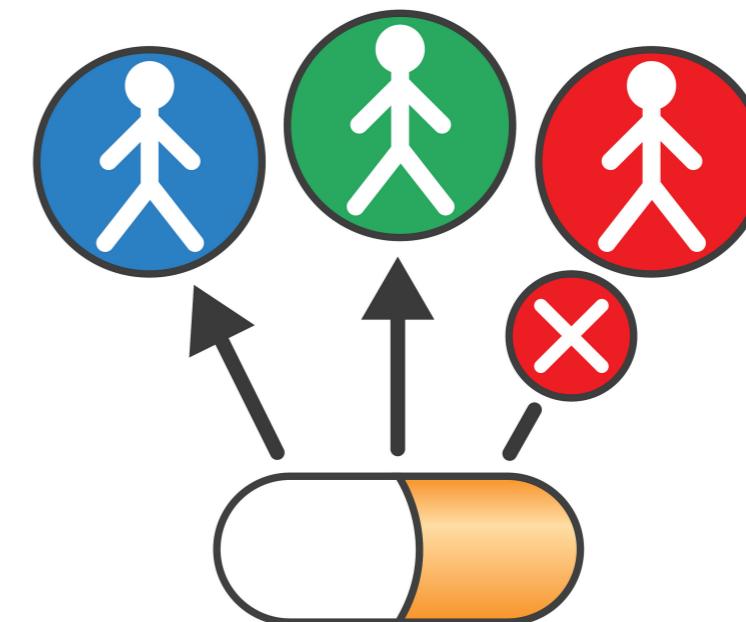
Group  
antidepressants

"Personalized treatment"?

Electroconvulsive therapy (ECT): 60-90% remission rate in treatment-resistant depression



Tests for differential diagnosis  
Tests for uni- vs. bipolar  
Predict individual treatment response



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Group 1-3 + Mirtazapin

Group 1-4 + 5

Group 1-4 + 6

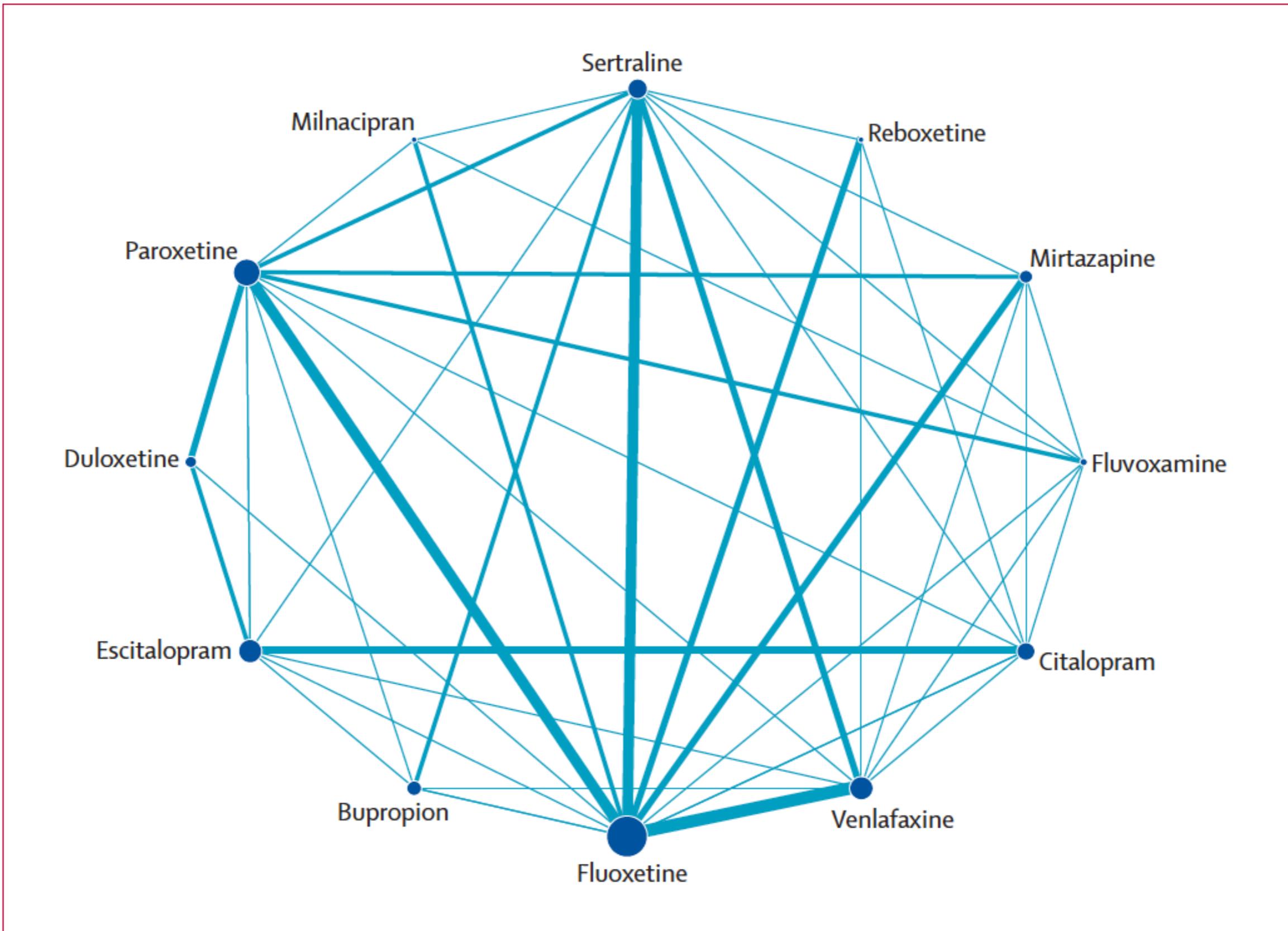
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Electroconvulsive therapy (ECT): 60-90% remission rate in treatment-resistant depression



Elect

**Figure 2: Network of eligible comparisons for the multiple-treatment meta-analysis for efficacy (response rate)**  
The width of the lines is proportional to the number of trials comparing each pair of treatments, and the size of each node is proportional to the number of randomised participants (sample size). The network of eligible comparisons for acceptability (dropout rate) analysis is similar.

Cipriani et al. (2009)

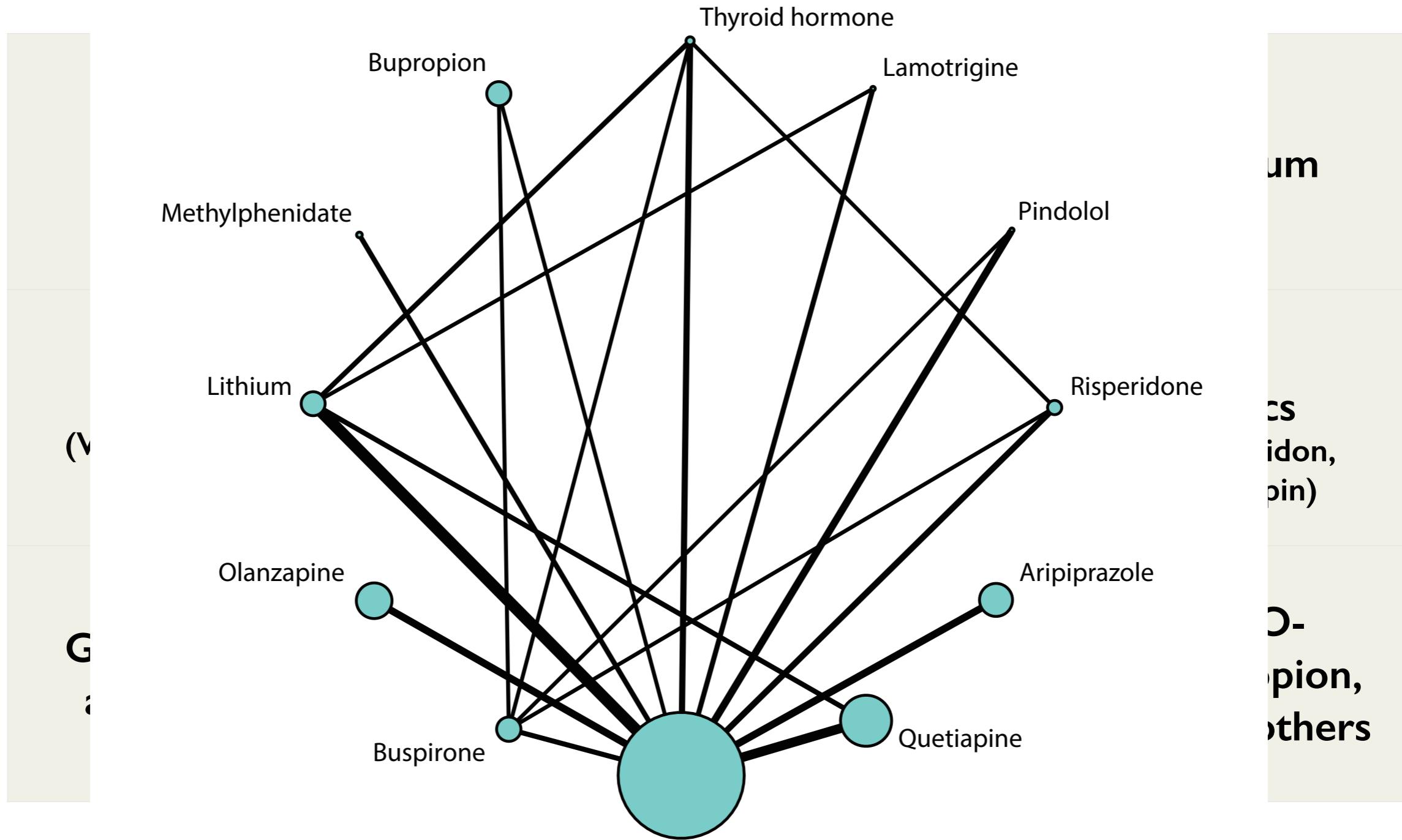
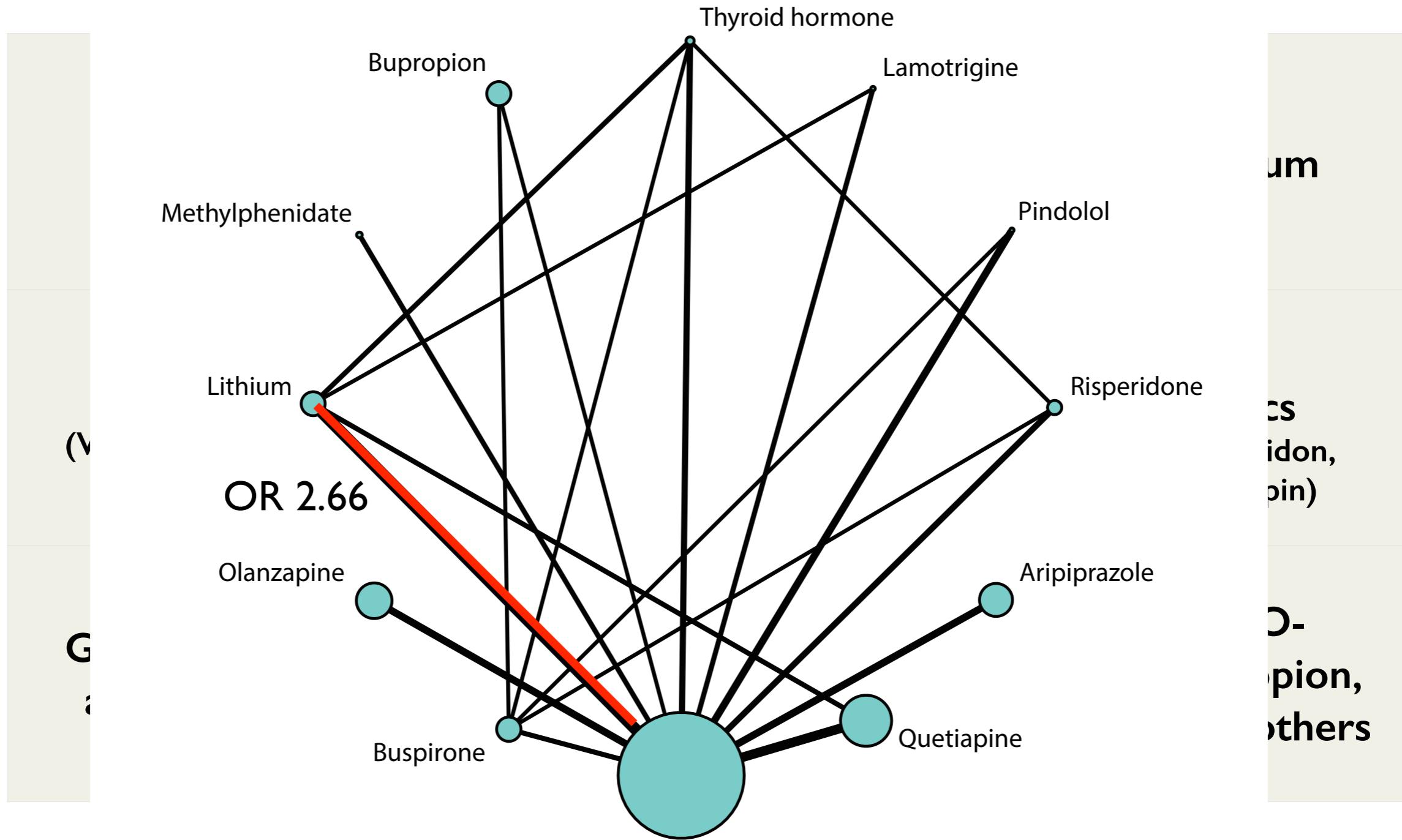
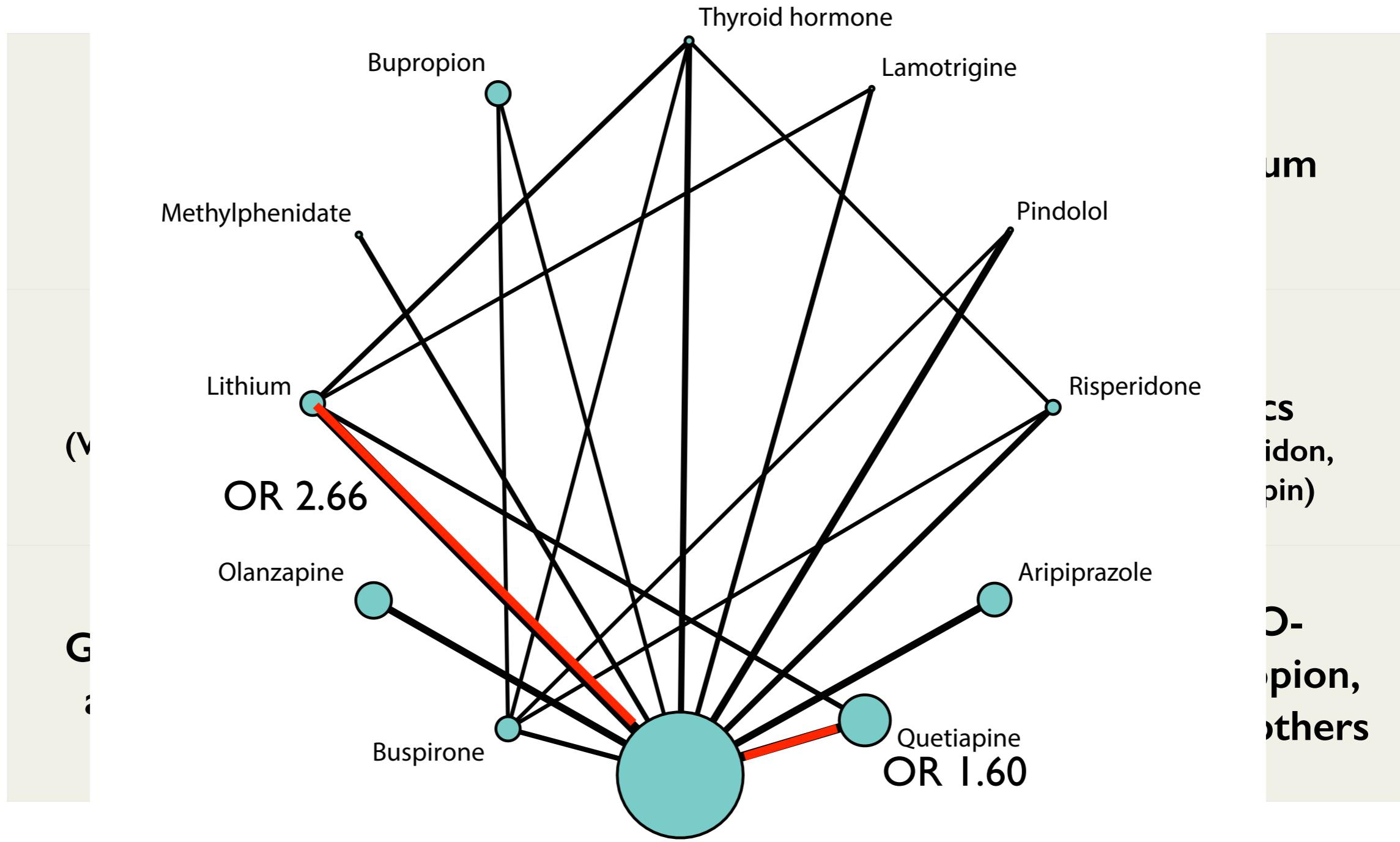
Figure 2. Network Plot of Eligible Comparisons for Primary Efficacy<sup>a</sup>

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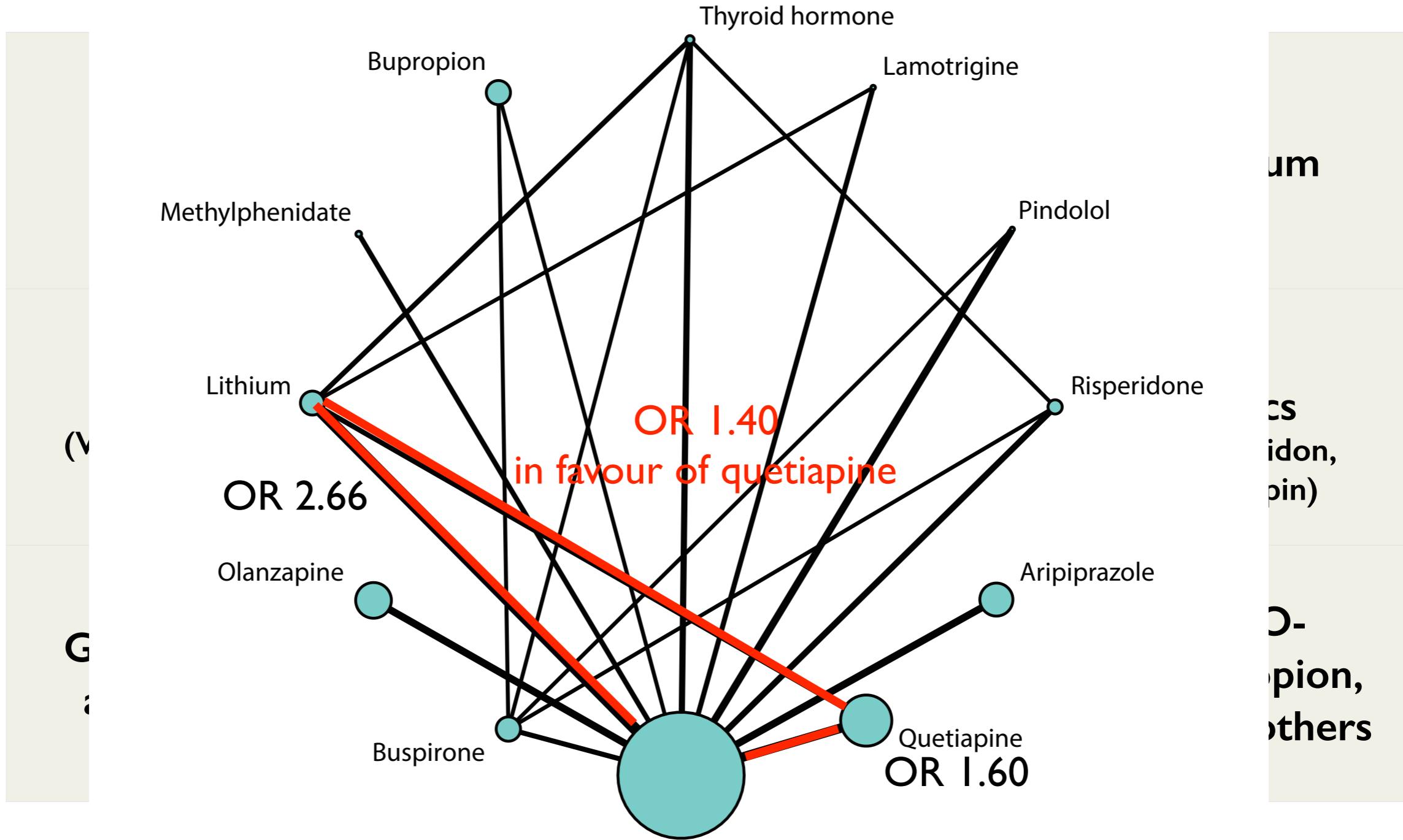
Electroconv

pression

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Electroconv

epression

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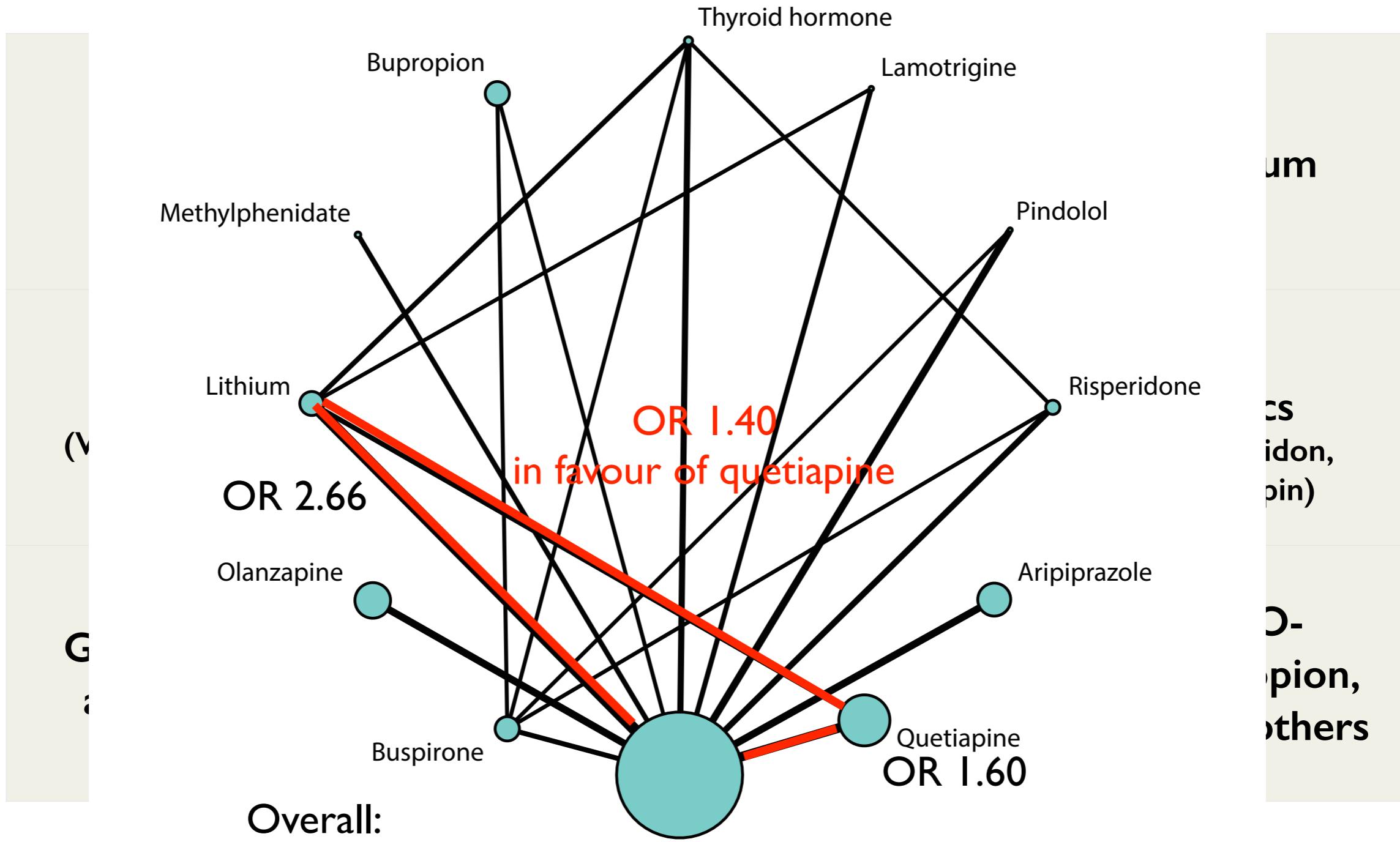
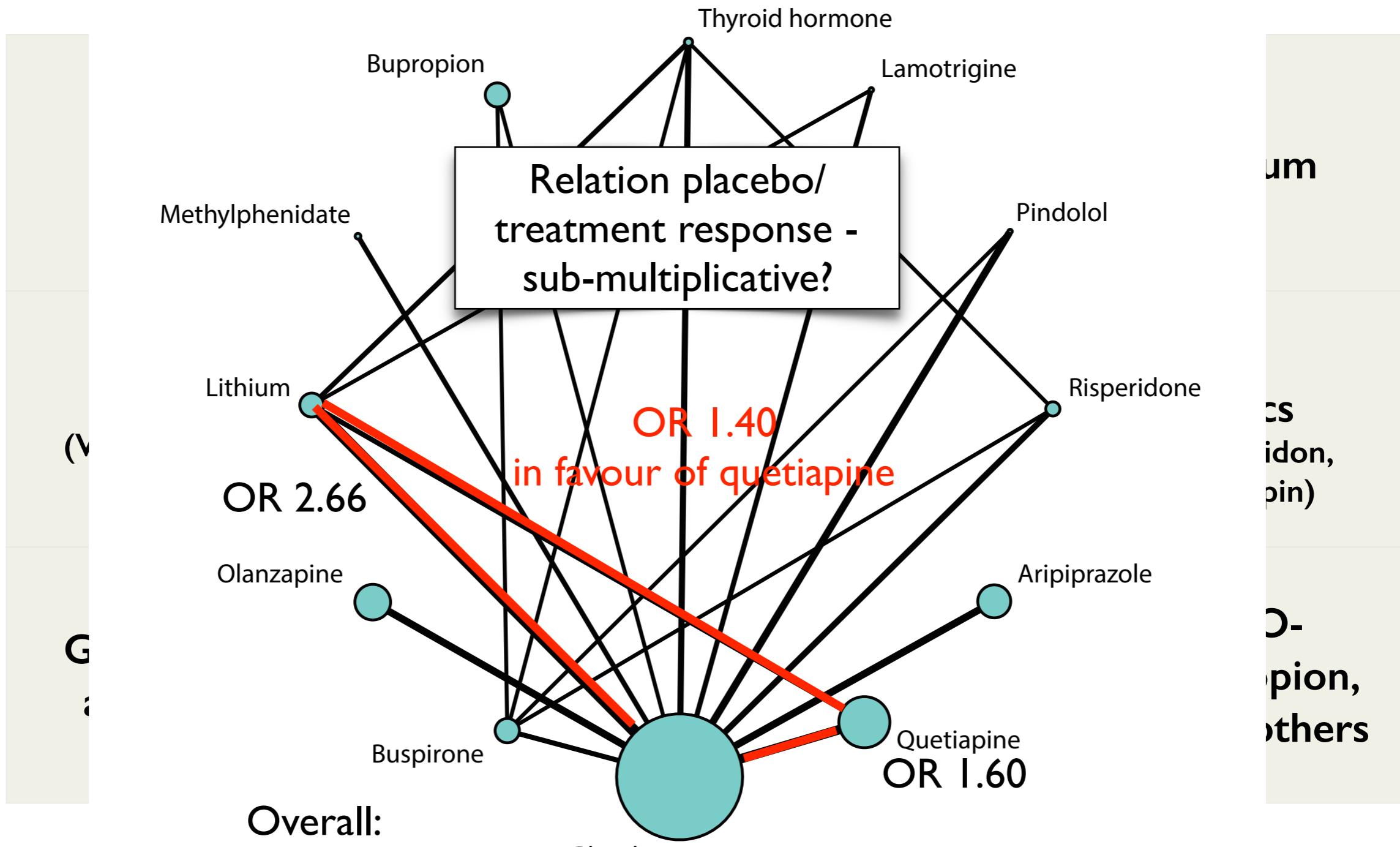
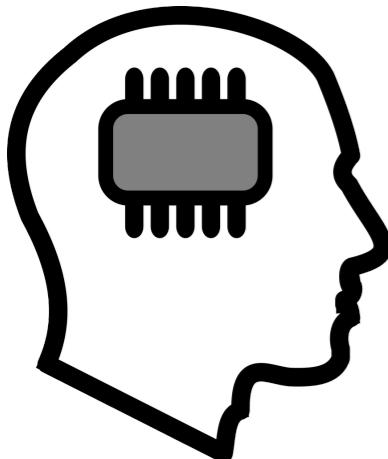
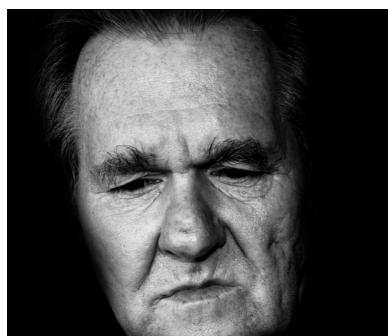
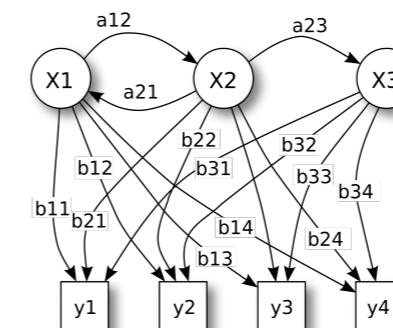
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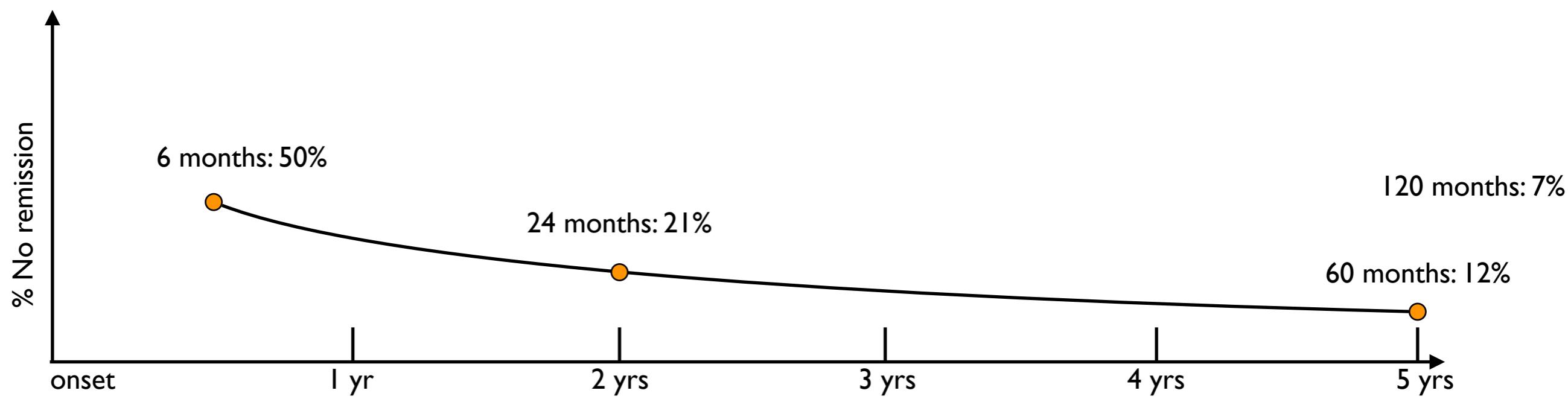


Tests for differential diagnosis  
Tests for uni- vs. bipolar  
Predict individual treatment response  
Improve models of placebo/treatment  
relation (BMS)



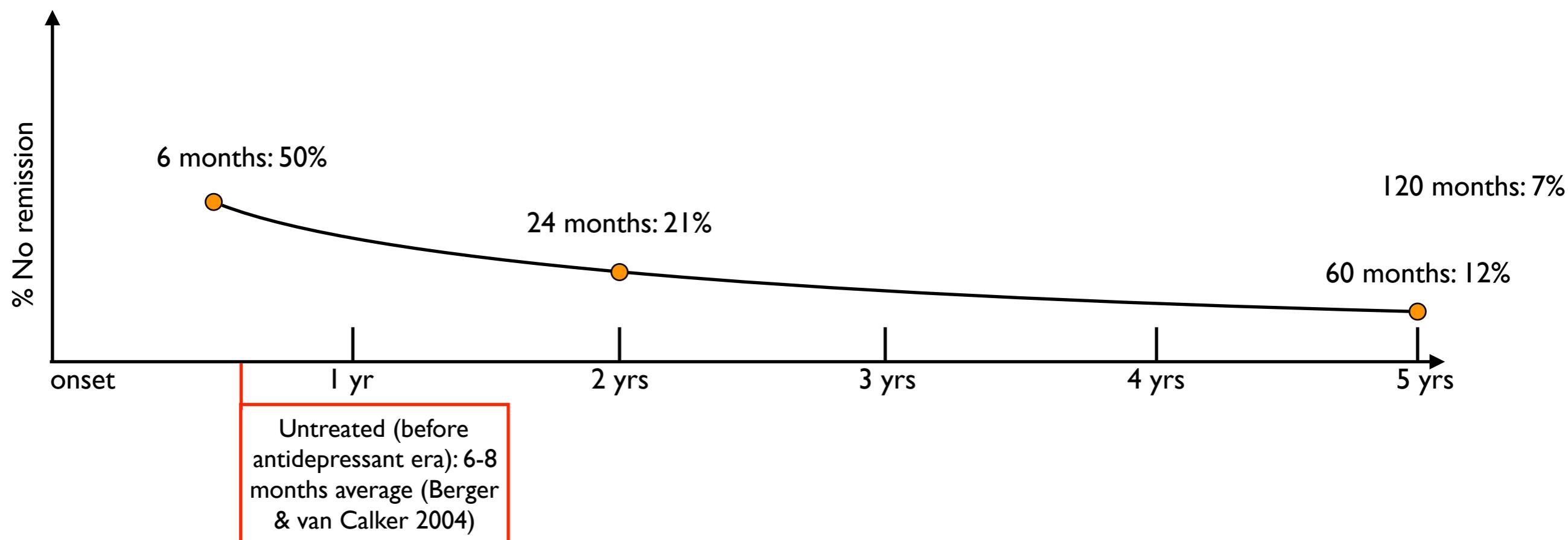
## Time course

100%



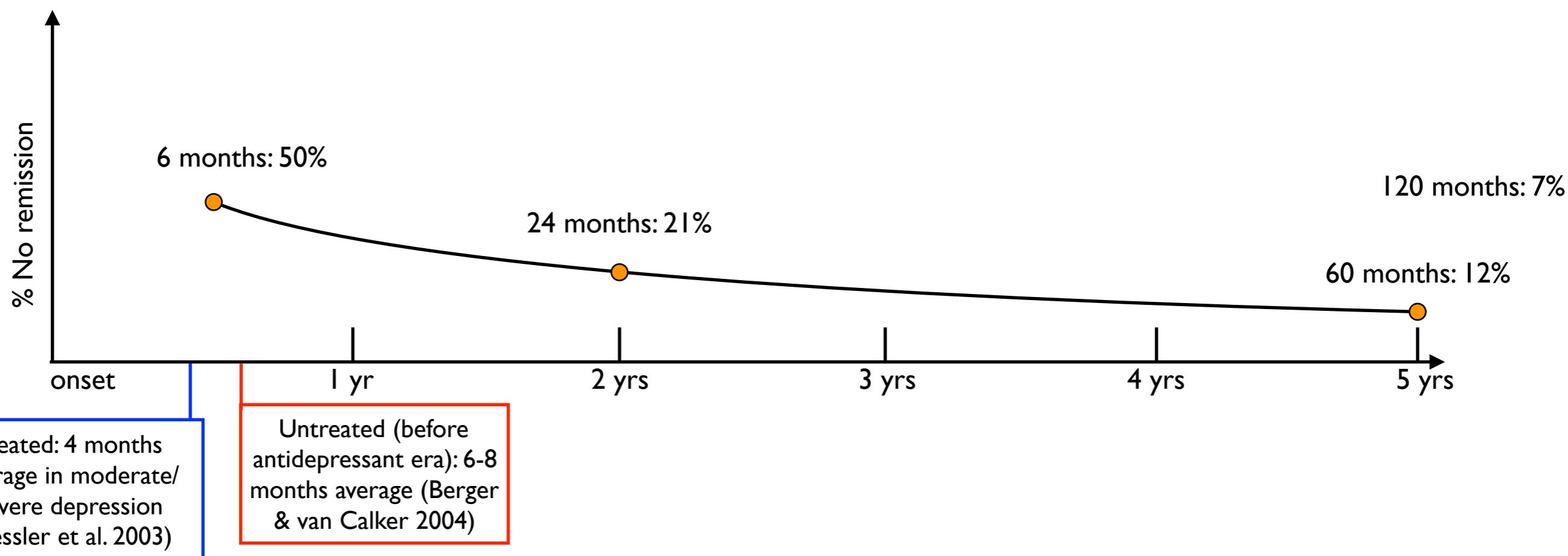
Keller et al., (1984, 1992, 1999)

100%



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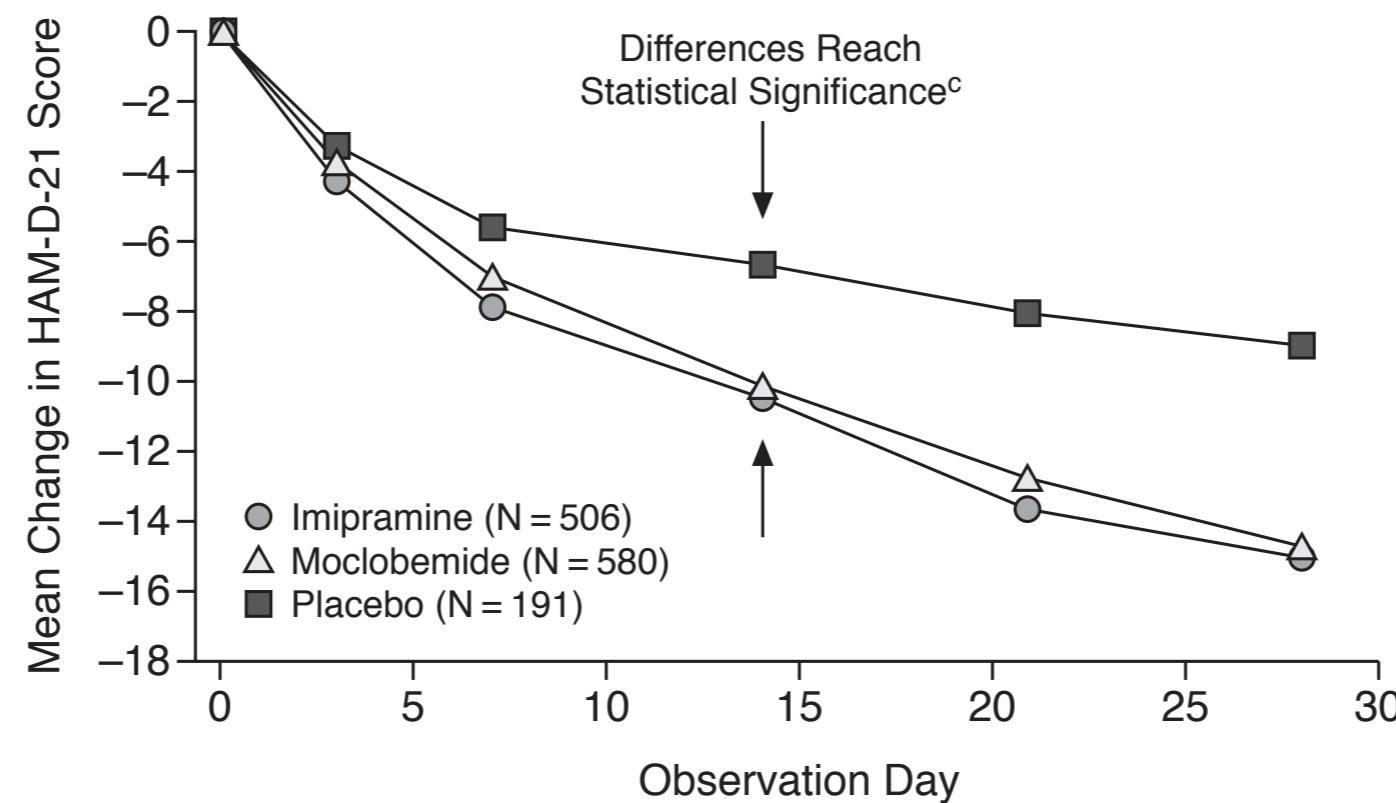
100%



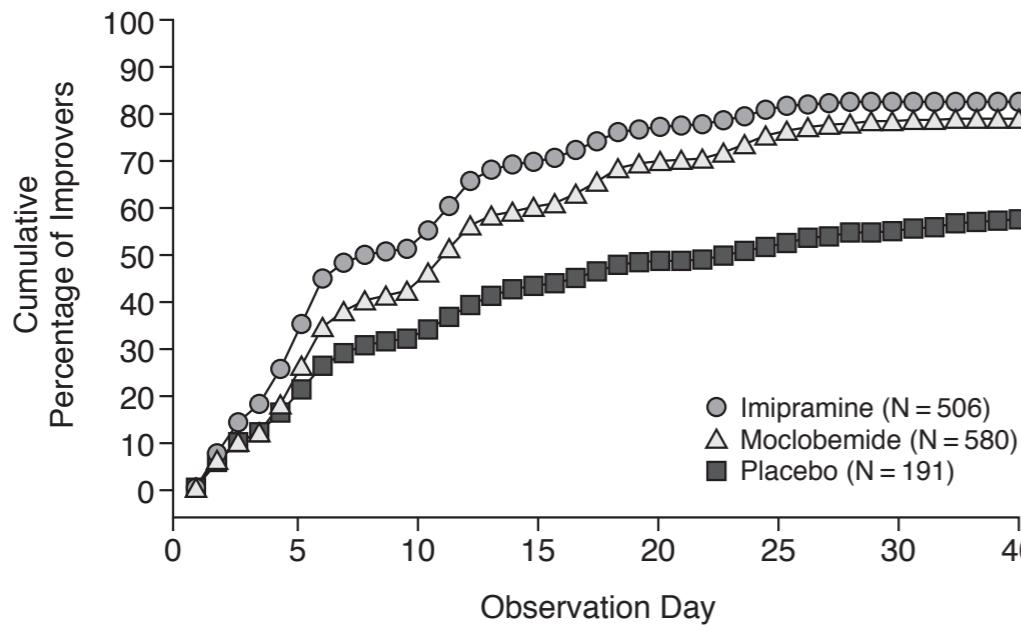
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# Response profile

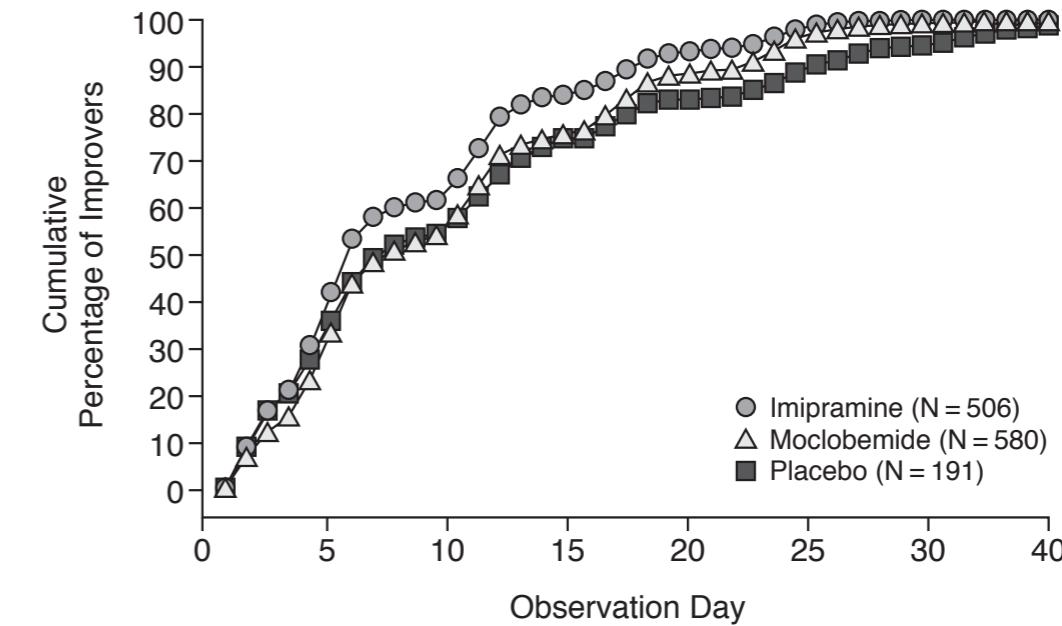
B.



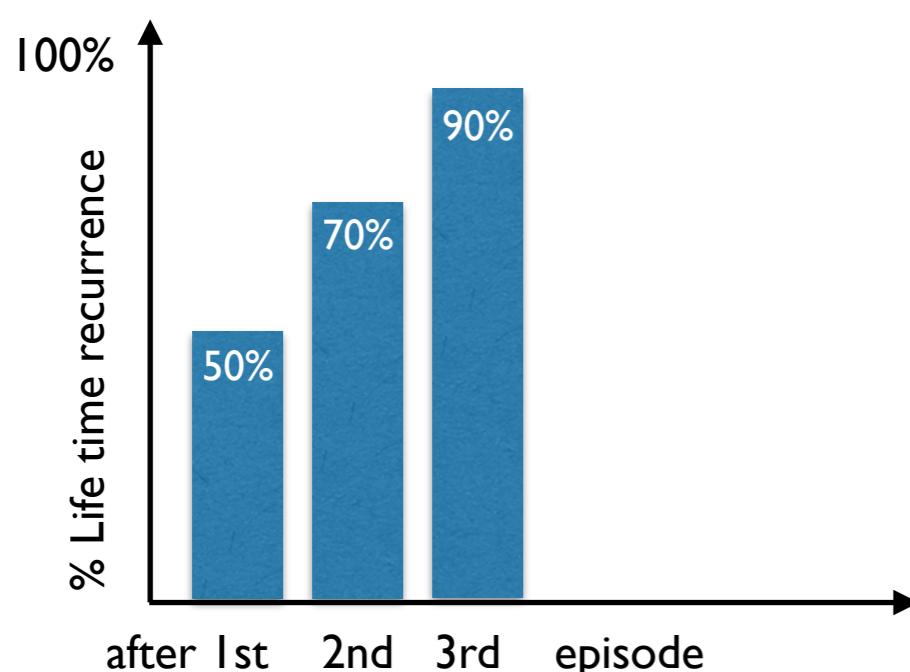
A.



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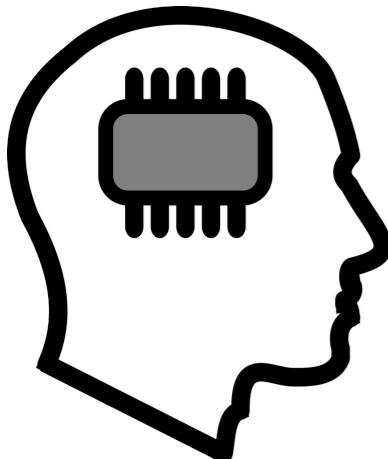
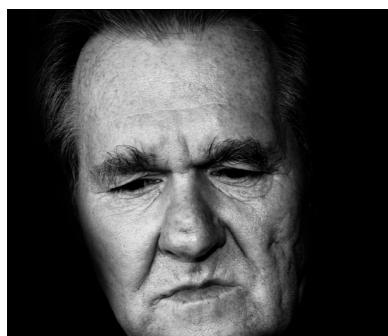


# Recurrence & mortality

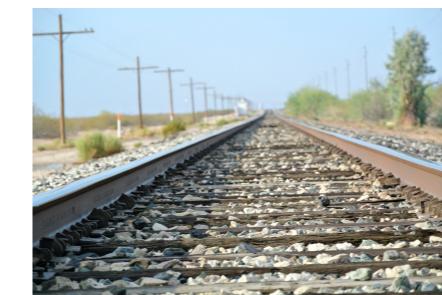


		Life time mortality from suicide
		8%
Any in-treatment due to suicidality		4%
Any in-treatment for depression w/o suicidality		
		5 year mortality from suicide
Meta-analysis		0.17%
Li treatment		1.48%
No Li treatment		

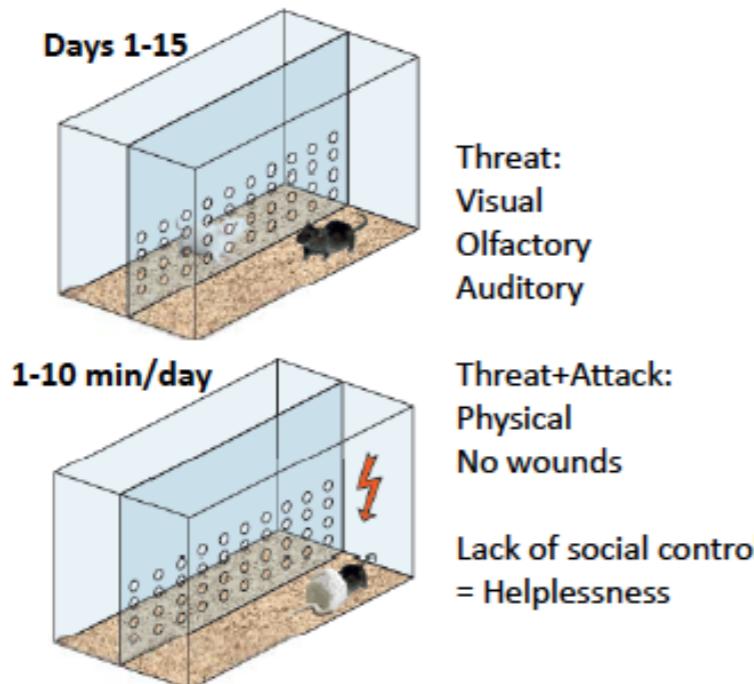
Harris & Barraclough (1997), Guzzetta et al. (2007), DGPPN guidelines



Tests for differential diagnosis  
Tests for uni- vs. bipolar  
Predict individual treatment response  
Improve placebo and treatment models  
(BMS)  
Predict spontaneous remission, recurrence,  
suicide



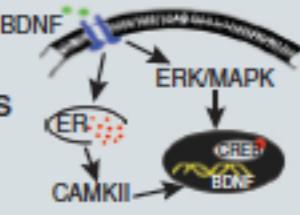
Early parental loss	3x increased risk 10x increased risk when before 9 years (but also increases schizophrenia risk)
Contryside	City > 500 000 vs. town/settlement < 20 000 2x increased risk
Partnership	No partner vs. partner 2x increased risk
First order relative with depression	1.5x increased risk



Pryce et al. (2011) *Pharm Therapeut* 132: 242

**Depression**  
Cognitive impairment  
Premature ageing  
Cardiovascular risk  
Wound healing complications  
Suppression of immune system

## Social Defeat Stress

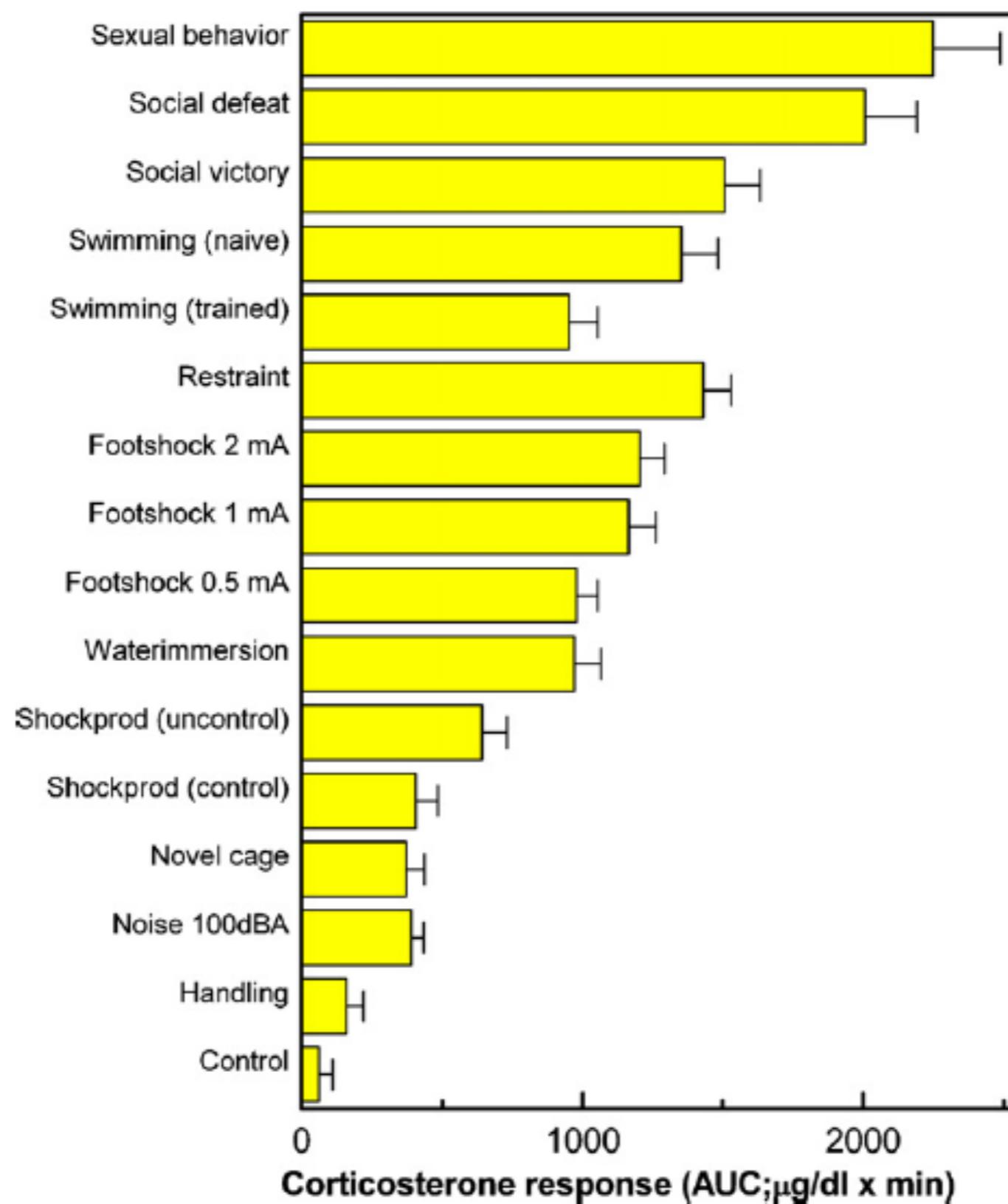
		Hippocampus
Behavior		↓ Spatial memory ↓ Spatial navigation
Networks		↓ Auditory-evoked potential ↓ Place cell
Neurons		↓ Dendrites
Synapses		↓ Spines ↓ LTP ↑ LTD
Molecules		↓ BDNF

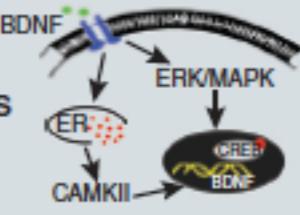
## Glucocorticoid hypothesis

Glucocorticoids have toxic effect on hippocampus (Sapolsky, McEwen and others)



# Cortisol response



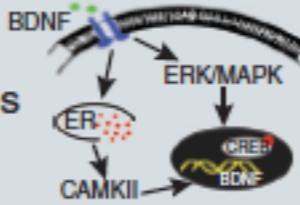
		Hippocampus
Behavior		↓ Spatial memory ↓ Spatial navigation
Networks		↓ Auditory-evoked potential ↓ Place cell
Neurons		↓ Dendrites
Synapses		↓ Spines ↓ LTP ↑ LTD
Molecules		↓ BDNF

## Glucocorticoid hypothesis

Glucocorticoids have toxic effect on hippocampus (Sapolsky, McEwen and others)

HOWEVER: cumulative Glucocorticoid dose does not explain effects of "chronic stress"

# Etiology: Role of stress

	Hippocampus	Amygdala	mPFC	
Behavior		↓ Spatial memory ↓ Spatial navigation	↑ Fear memory ↑ Anxiety	↓ Working memory ↓ Fear extinction
Networks		↓ Auditory-evoked potential ↓ Place cell	↑ Auditory-evoked potential	?
Neurons		↓ Dendrites	↑ Dendrites	↓ Dendrites
Synapses		↓ Spines ↓ LTP ↑ LTD	↑ Spines ↑ LTP	↓ Spines ↓ LTP
Molecules		↓ BDNF	↑ BDNF	?

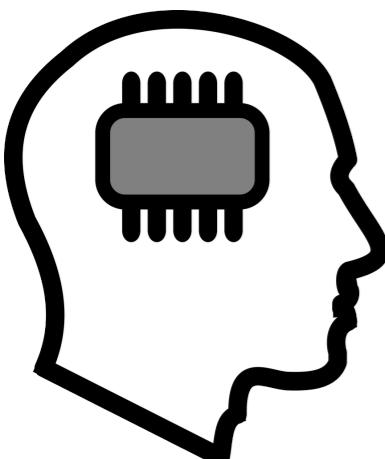
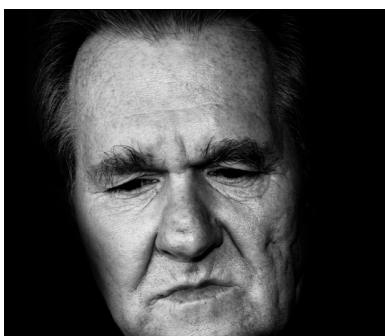
# Cognitive impairment

- associated with illness duration but not symptom severity
- does not remit within 8-week treatment (RCT escitalopram, sertraline, venlafaxine)
  - is not associated with symptom remission

(Shlyanski et al. 2016 Lancet Psychiatry: iSPOT-D study, 1008 outpatients)

- work productivity in first 6 treatment weeks predicts depression outcome after 3 and 7 months even when controlling for symptom remission at week 6

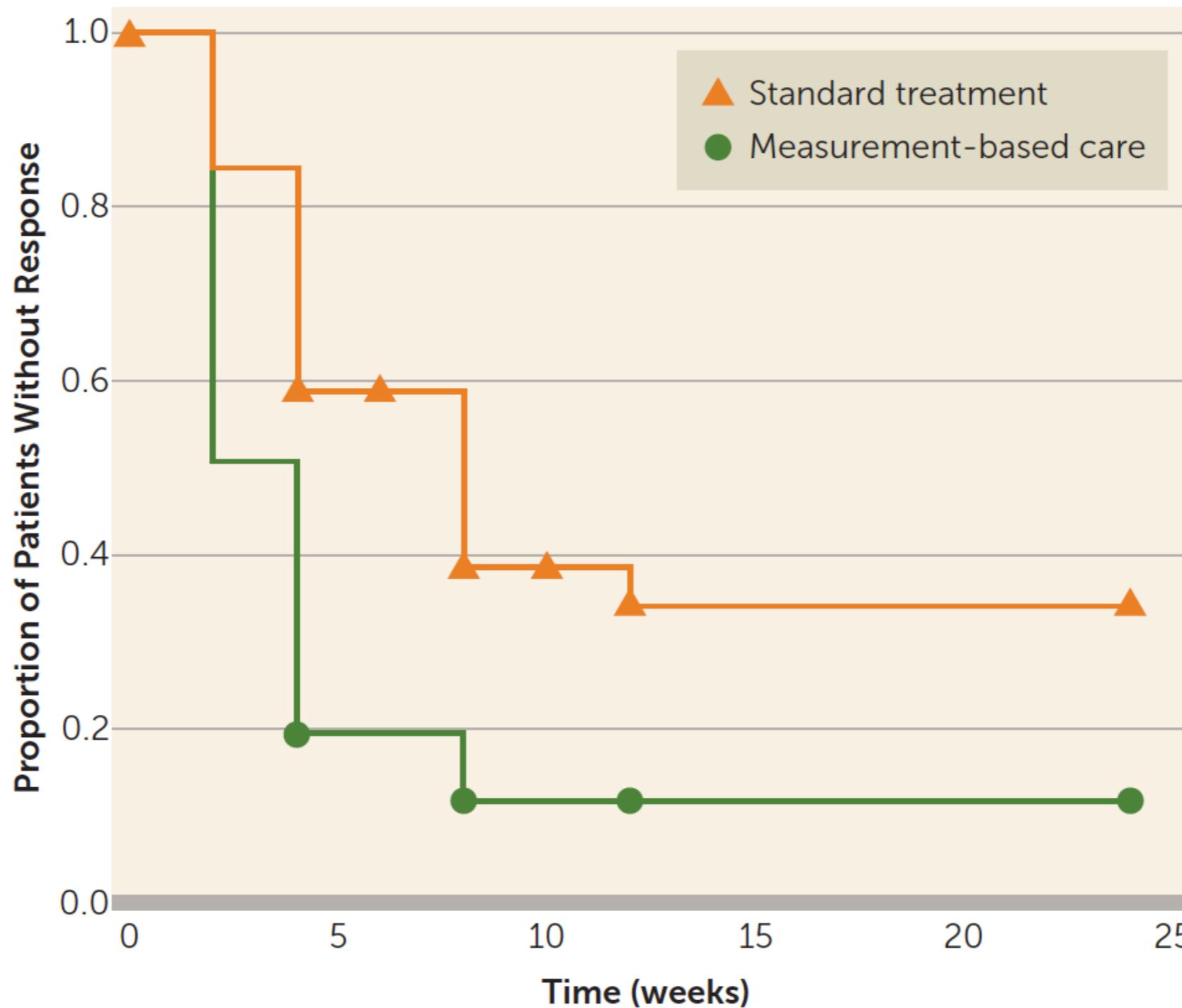
(Jha et al. 2016 Am J Psychiatry)



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# Algorithm based care

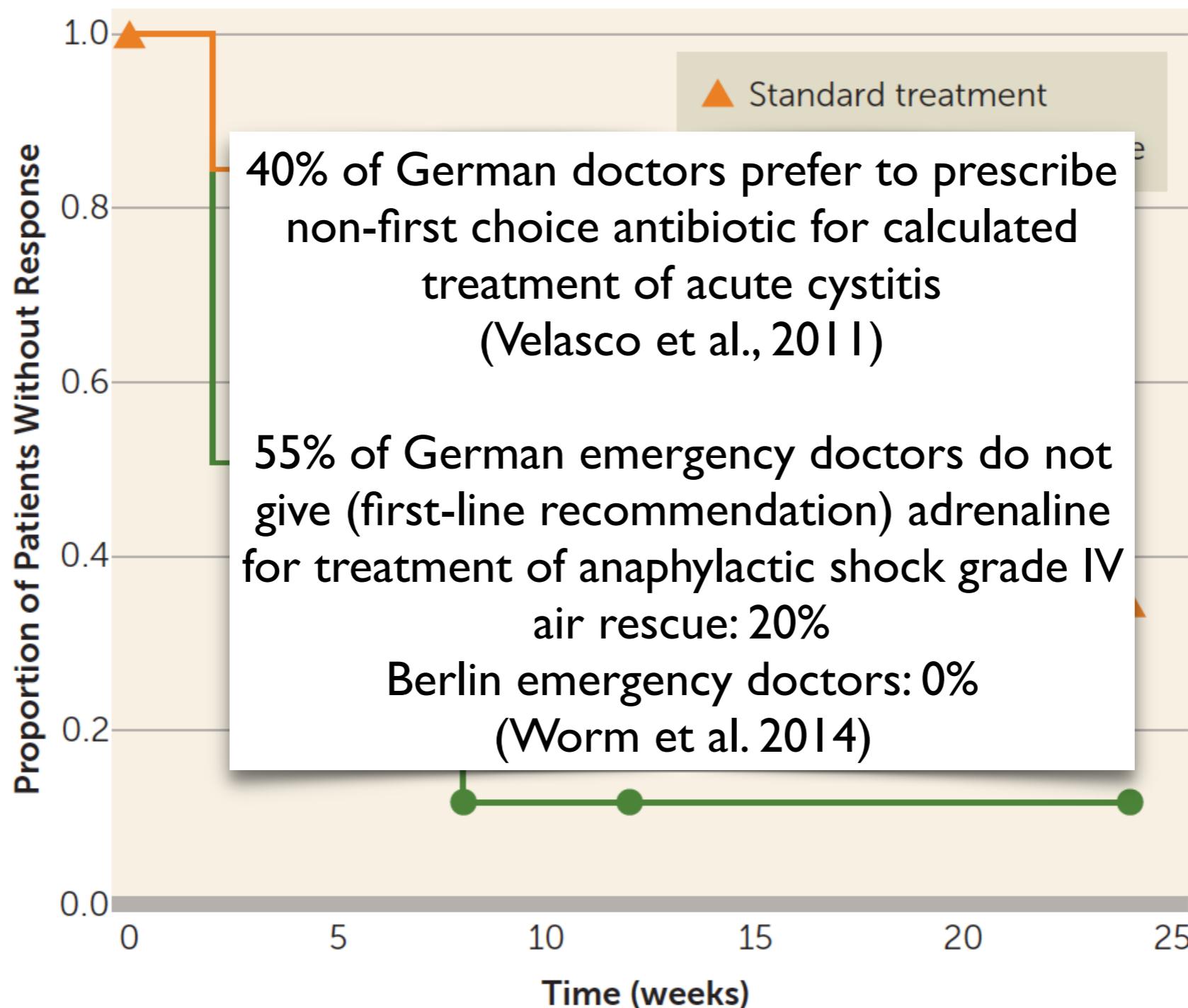
A. Estimated Mean Time to Response



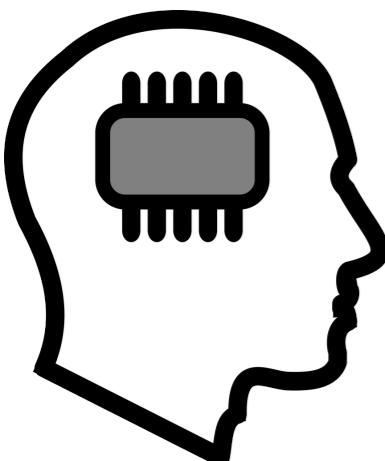
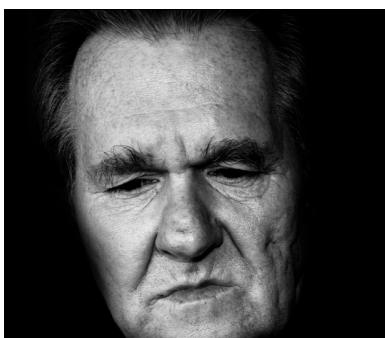
Texas algorithm project, German algorithm project, STAR\*D

# Algorithm based care

## A. Estimated Mean Time to Response



Texas algorithm project, German algorithm project, STAR\*D



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Communicate!  
Make a difference!