



Treatment of Anxiety Disorders

Where is the room for improvement?

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Disclosures

Advisor: PRIMA Barn & Vuxen Psykiatri AB
(private health care provider)

Speaker: Shire, Lundbeck, Pfizer Asia, The
Swedish Police Academy, The Swedish
Courts Academy, Scania Health Care



Objective

To obtain a clinical and research update on the current use of anxiolytics (and CBT) in patients with morbid anxiety.

Outline

Pharmacoepidemiology

GAD, Social Anxiety, Panic Anxiety

The meaning of guidelines

Anxiety as a companion in somatic disease

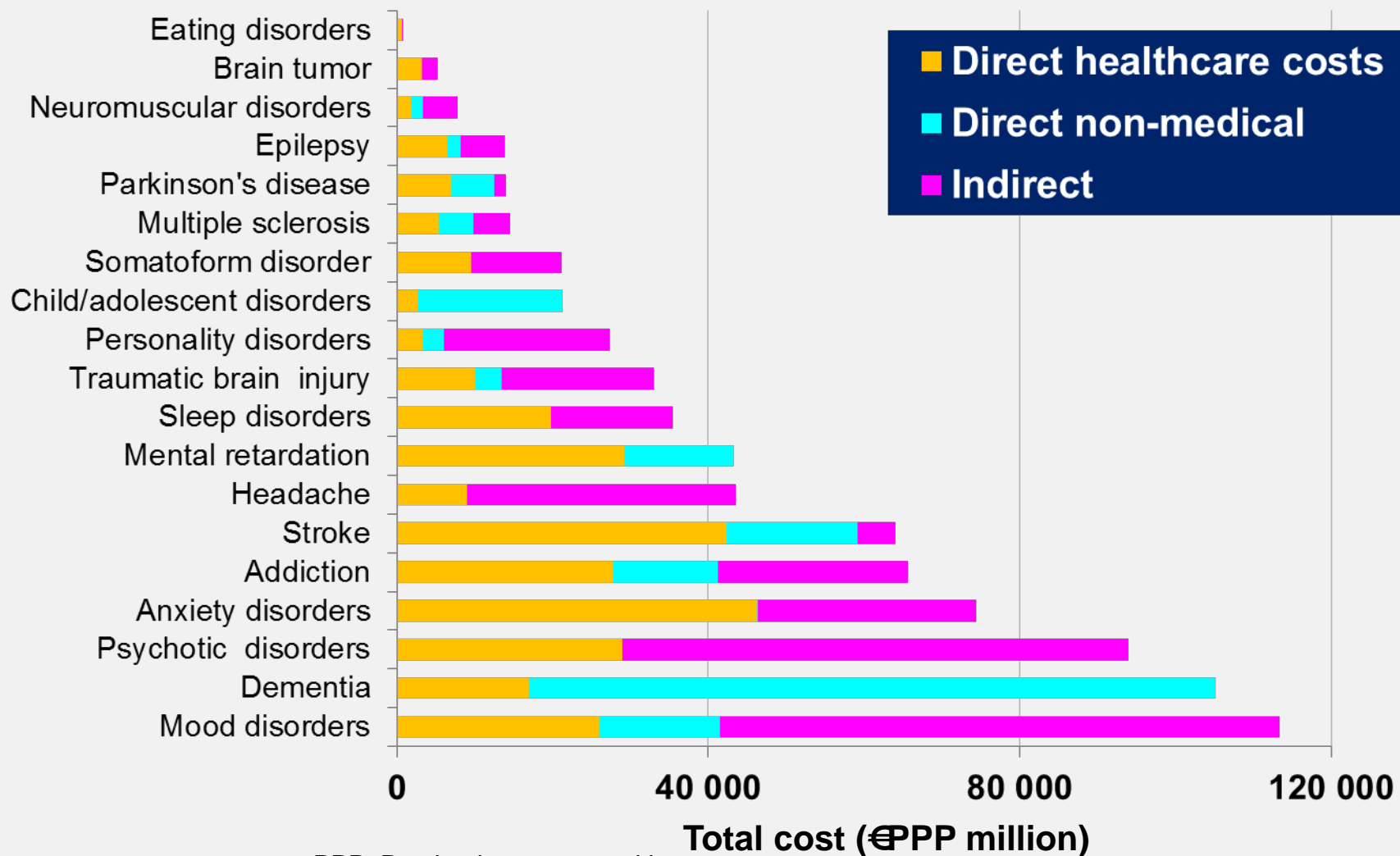
Treating the elderly

Utility of benzodiazepines

Ethnicity and psychopharmacology

Adherence to treatment

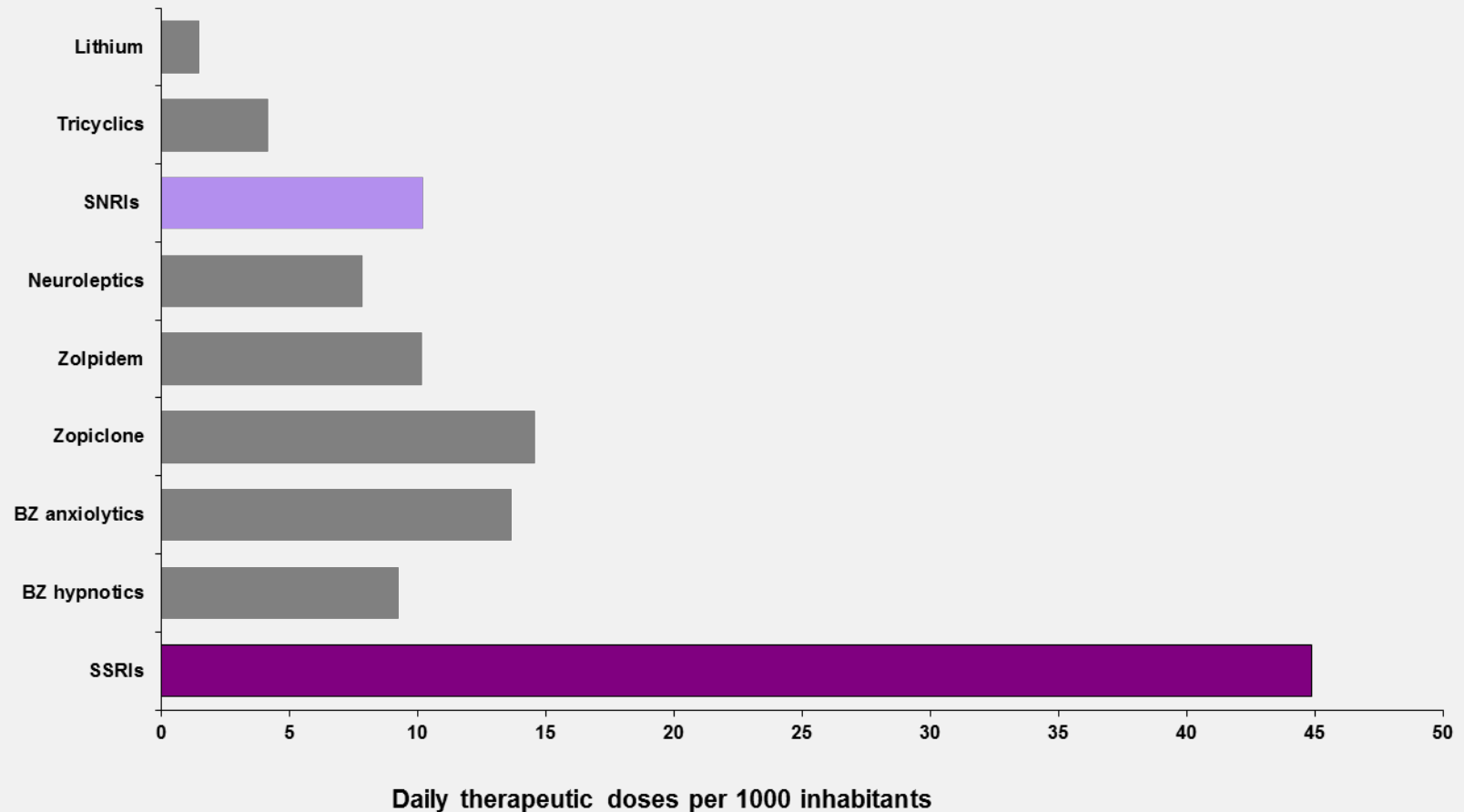
Total Cost of Brain Disorders in Europe 2010



PPP: Purchasing power parities

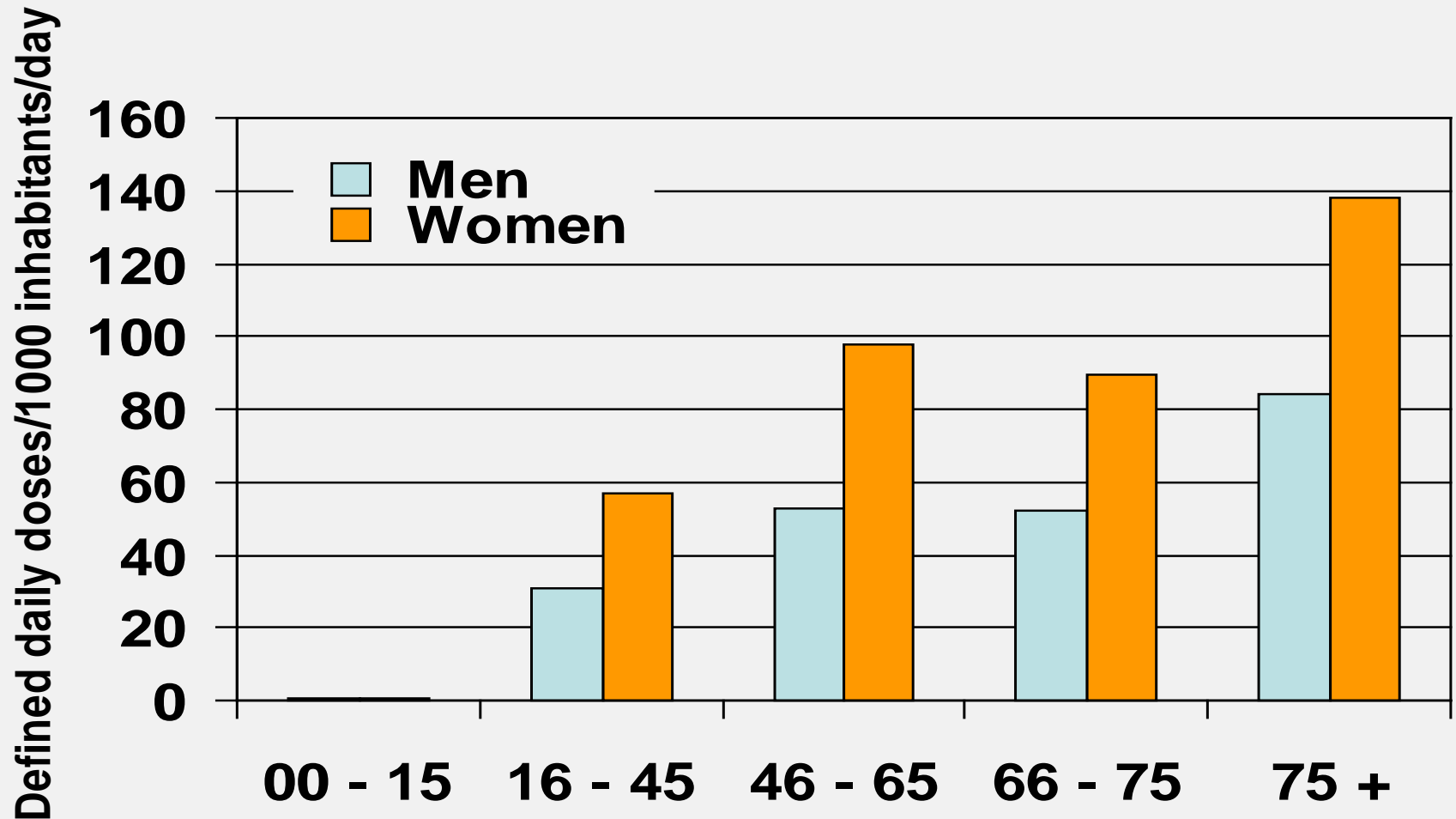
Gustavsson et al. Eur Neuropsychopharmacol 2011; 21: 718-779

Prescriptions in outpatient care in Sweden, 2002



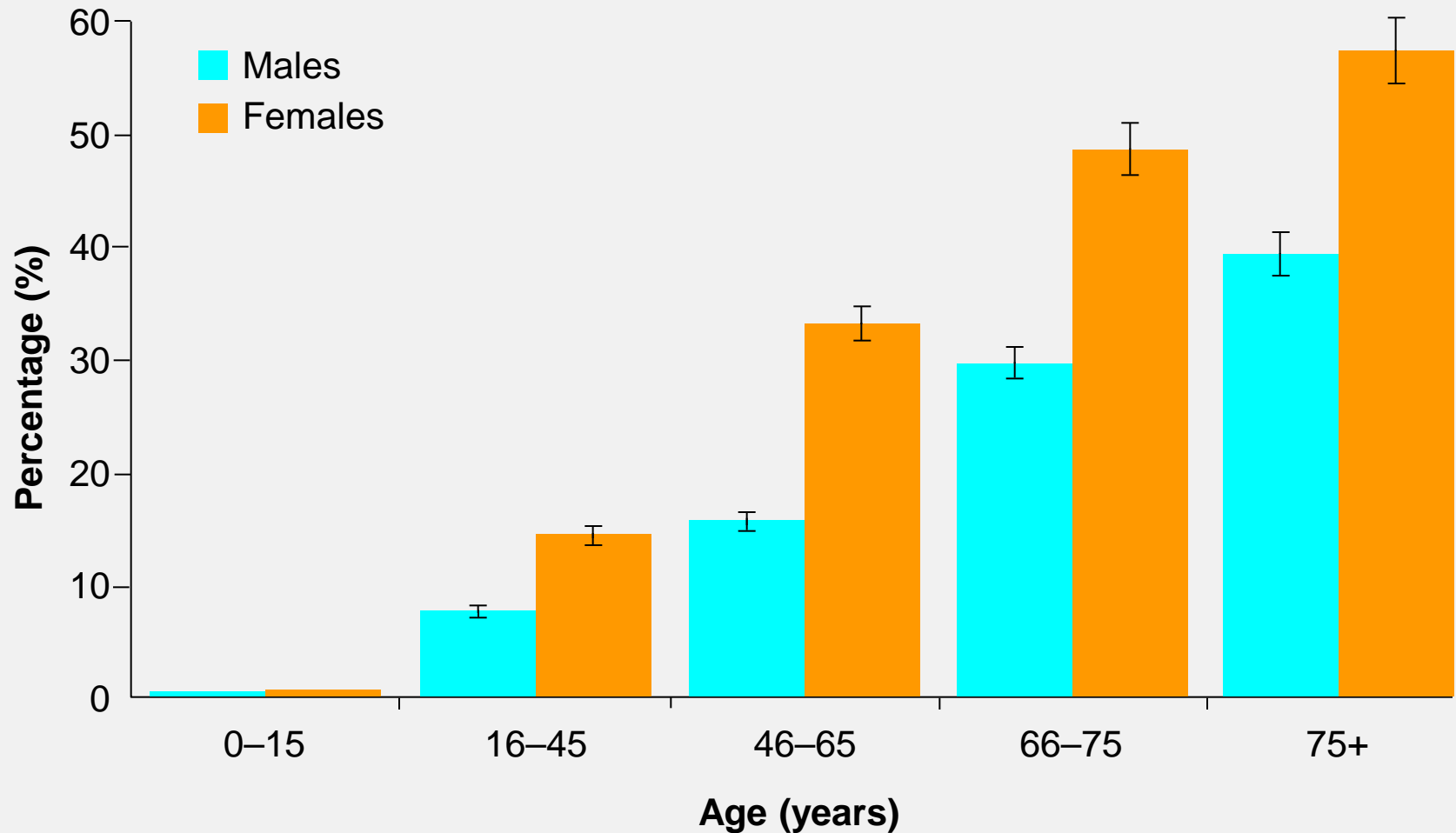


ANTIDEPRESSANT PRESCRIBING IN OUTPATIENT CARE, SWEDEN 2007





Antidepressants/anxiolytics in primary care - Piedmont (pop. 1,057,053)



THE AGE OF ANXIETY

W. H. Auden



A RANDOM HOUSE BOOK

"Now is the age of anxiety", 1947



Donald F. Klein
DSM-III 1980

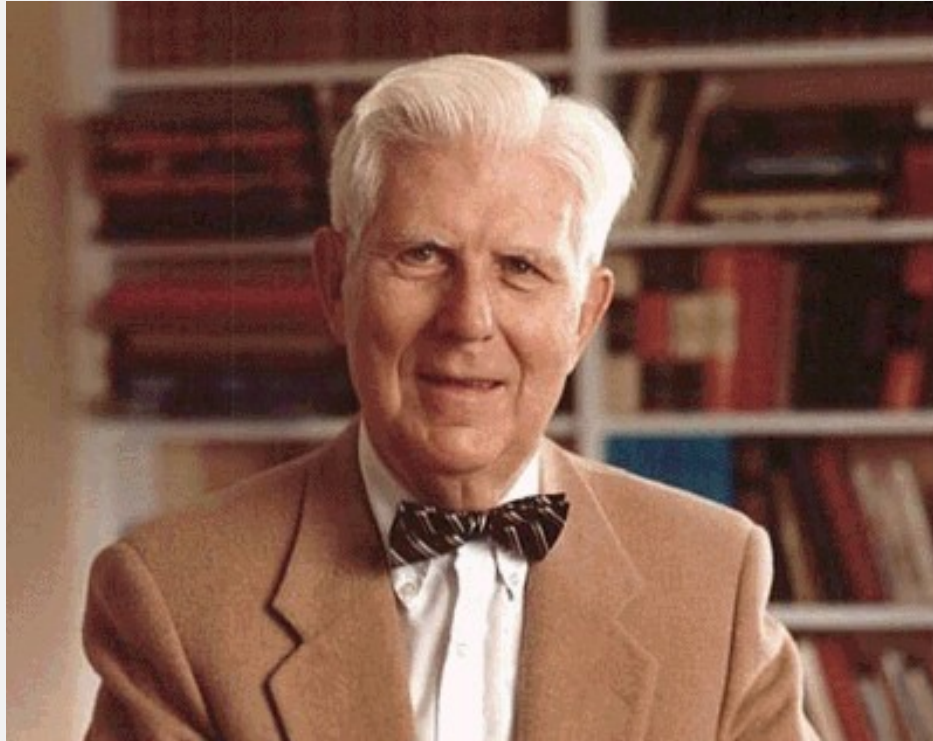
**Gittelman-Klein R, Klein DF. Controlled
imipramine treatment of school phobia.
Arch Gen Psychiatry 1971;25:204-207**



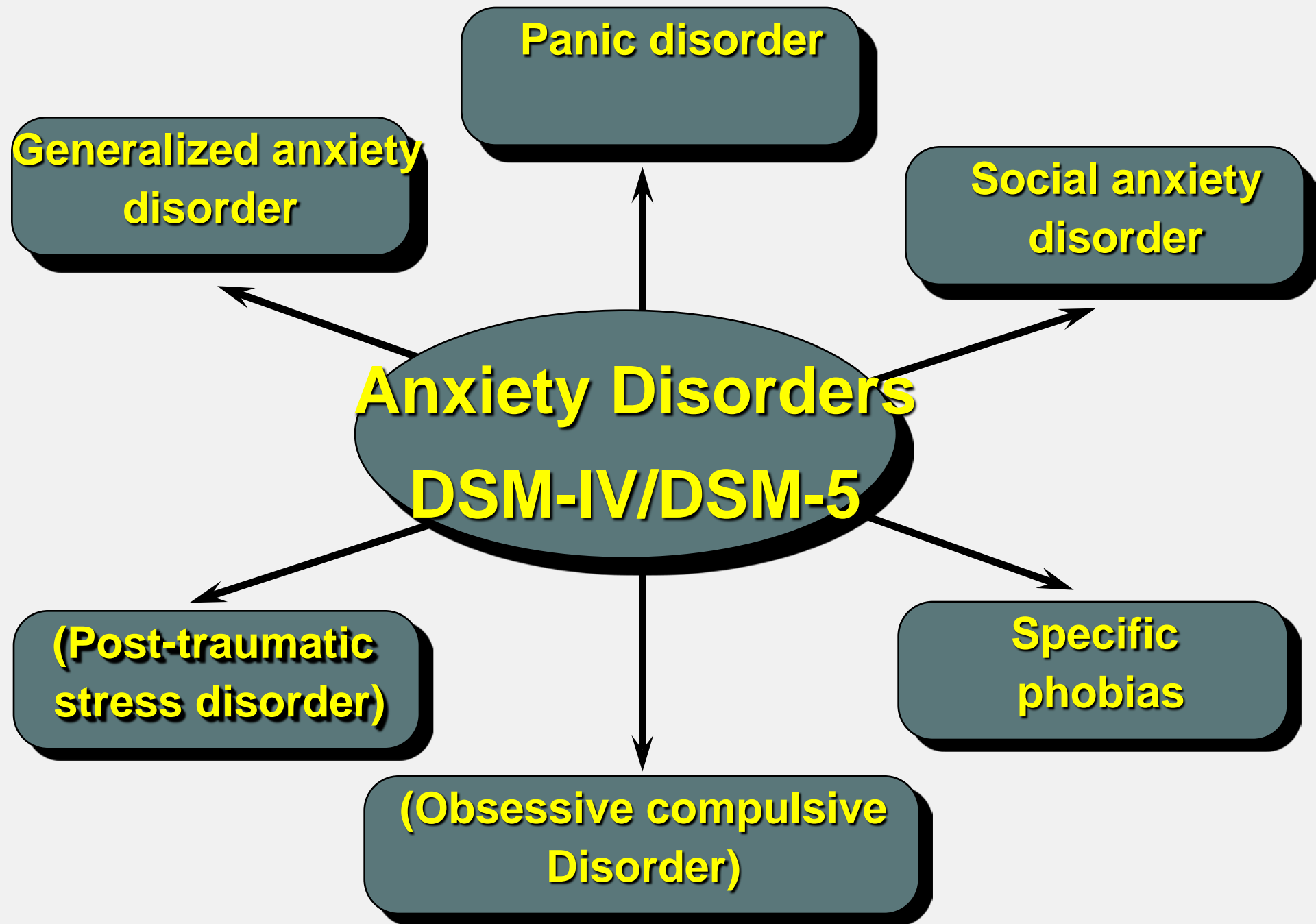
Zimelidine patent 1972



Carlsson A, Wong DT. Life Sci 1997;61:1203



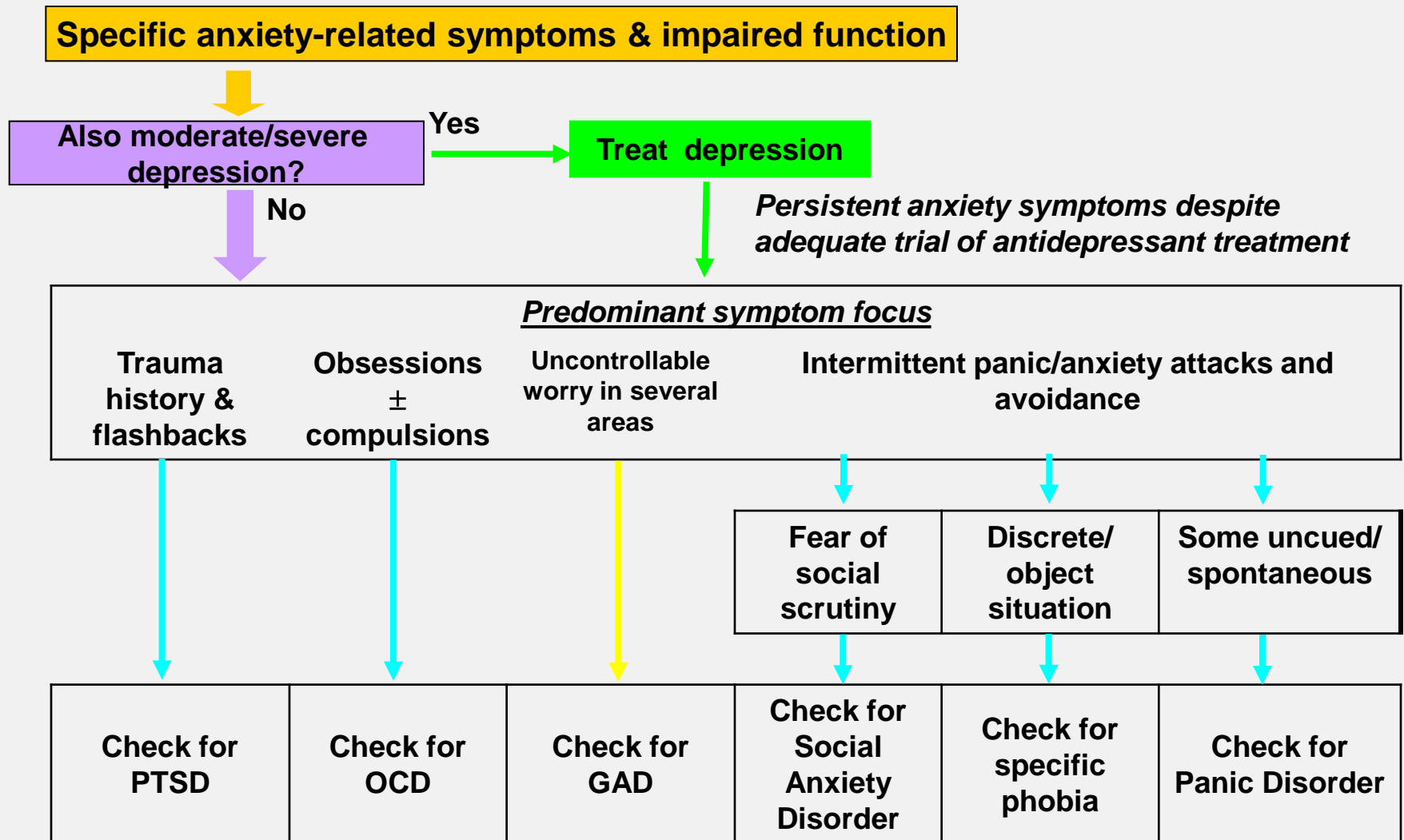
Aaron Beck, the father of cognitive therapy
The Lasker Award 2006




Specific phobias



Guidance for exploring a suspected anxiety disorder





1-year prevalence (%; CI) for anxiety disorders amenable to treatment

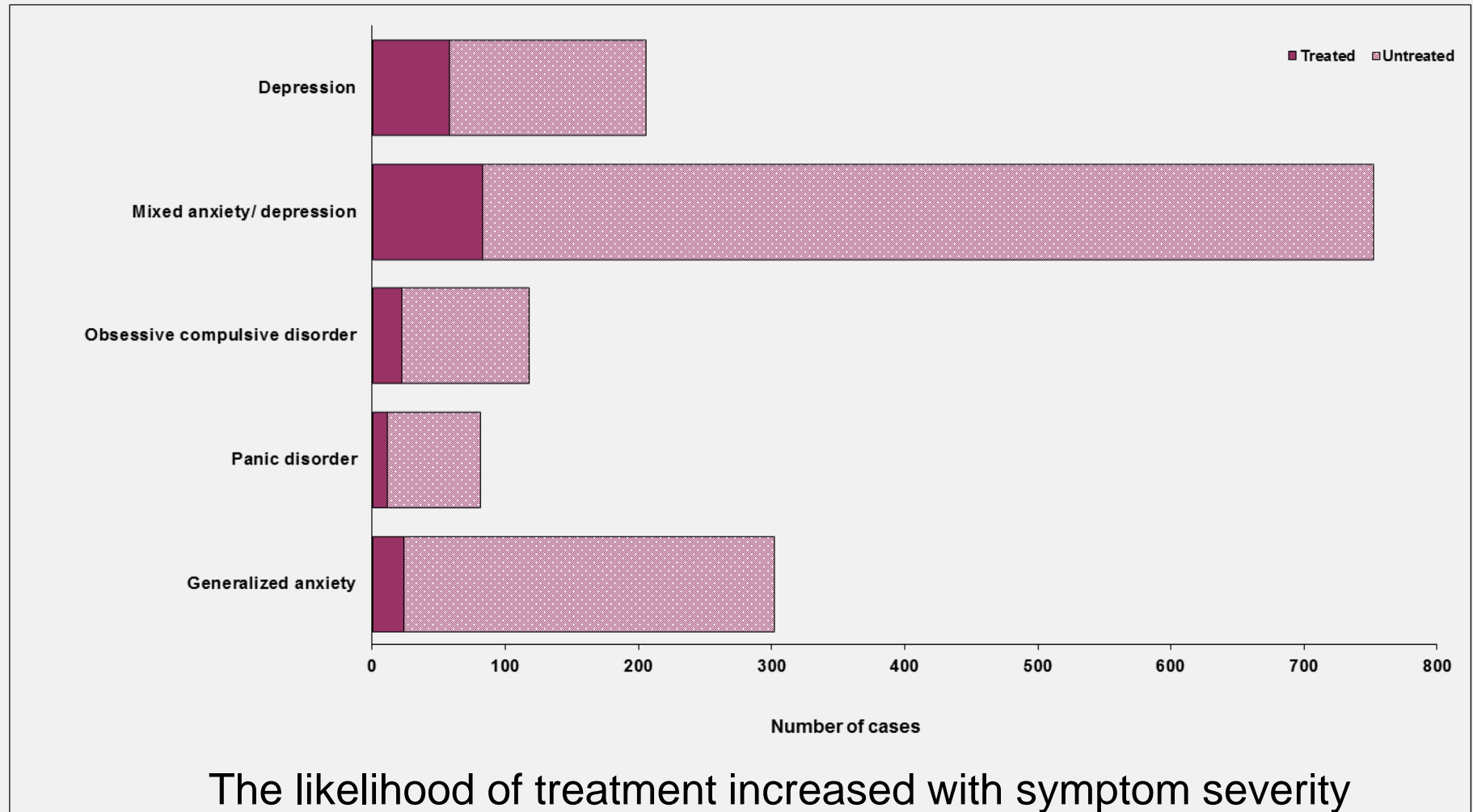
U.S.

Social anxiety disorder	3.7	(3.1 - 4.3)
Panic disorder	1.7	(1.1 - 2.3)
GAD	2.8	(2.2 - 3.4)

Canada

GAD	2.6	(2.3-2.8)
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Treatment for Anxiety/Depression in the UK ICD-10 Survey (N=10,108)



Generalized Anxiety Disorder



C.A. Friedrich: Seabreeze 1804, from J. Lohse, Neustadt

Do you see a barrier or a floating asset?

YOU WORRY TOO
MUCH... IT DOESN'T
DO ANY GOOD...

IT DOES FOR
ME... 95% OF
THE THINGS I
WORRY ABOUT
NEVER HAPPEN!

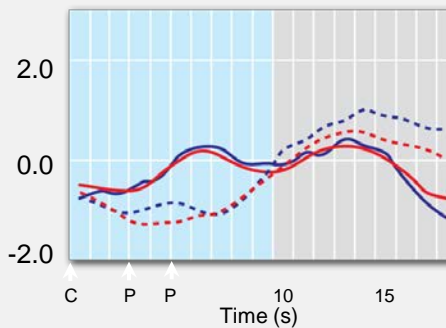
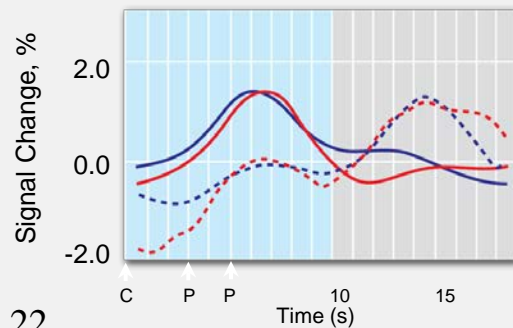
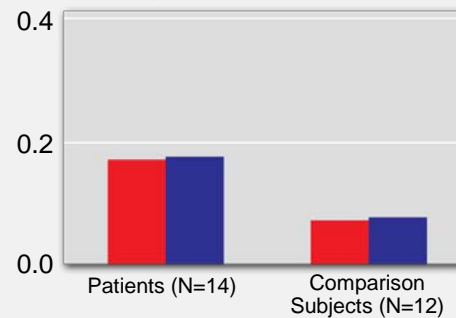
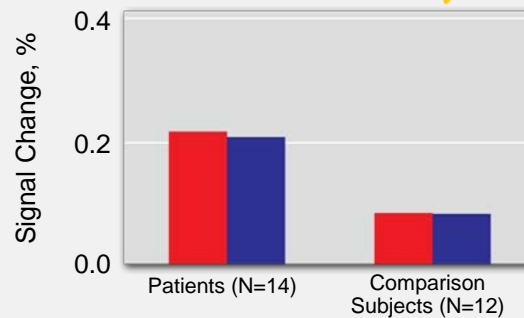
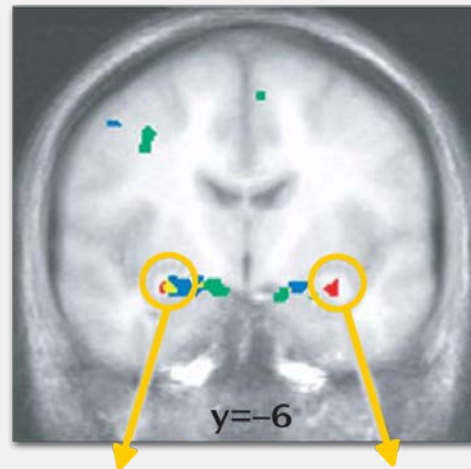




Diagnostic Criteria for GAD

- Excessive worry that is uncontrollable and interfering
- Accompanied by being (at least 3 items)
 - Restless
 - Tense
 - Fatigued
 - Unable to concentrate
 - Irritable
 - Sleepless
- Directly causing distress/impairment
- Present most of the time for >6 months
- Not due to medication, illness, or substance abuse

Anticipatory amygdala activity in GAD: fMRI findings



- Patients, aversive trial
- Patients, neutral trial
- ... Comparison subjects, aversive trial
- ... Comparison subjects, neutral trial

Neural correlates of worry in GAD; an fMRI study. Milano and Pavia

Worry in normal subjects and in subjects with GAD
is based on activation of the medial prefrontal and
anterior cingulate regions.

Sympathetic activation in GAD

During a 24 hour measurement of skin conductance, GAD patients failed to periodically reduce sympathetic tone.



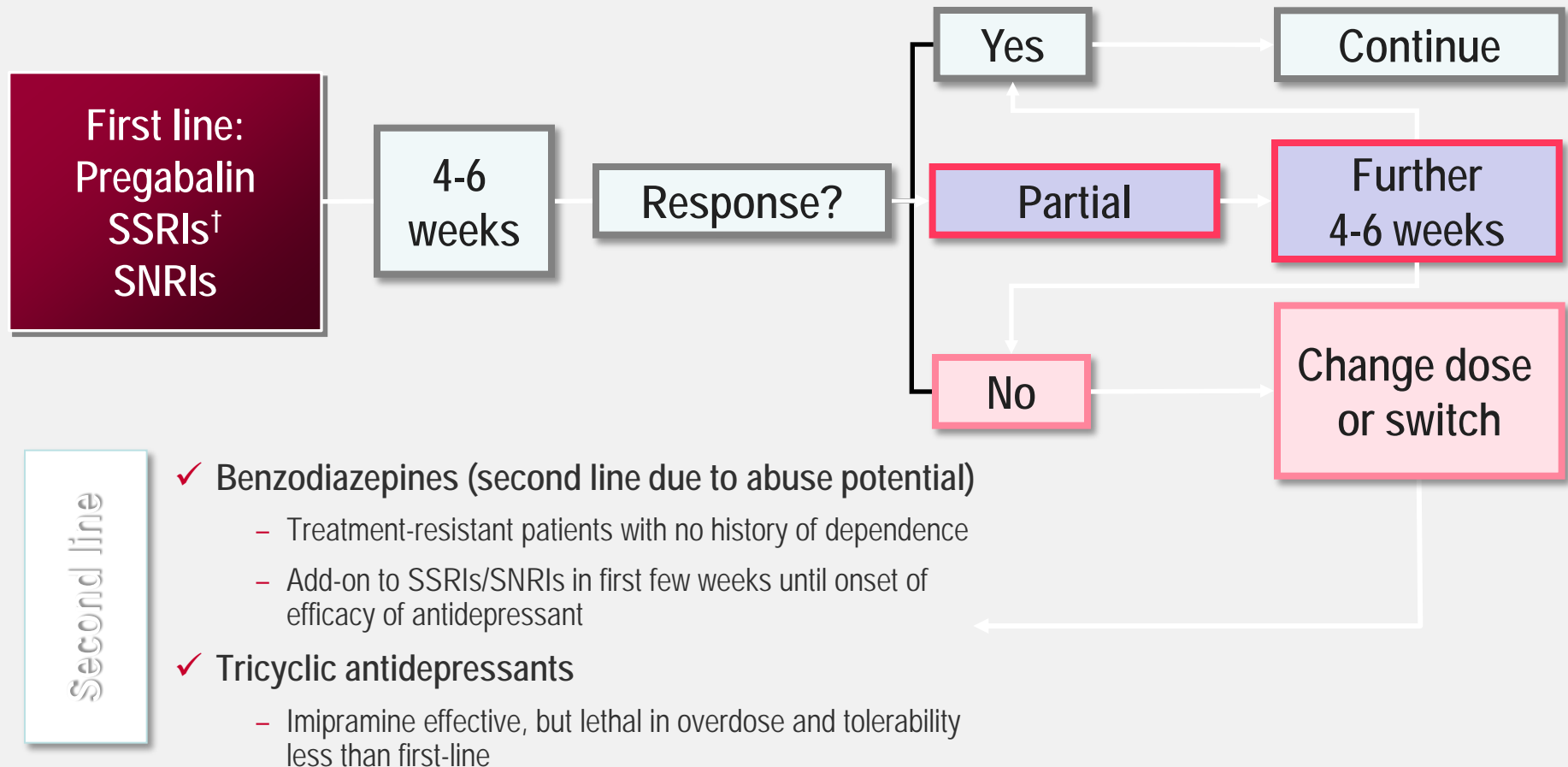
Cellular aging, telomere length

...robust associations of depressive and anxiety disorders with shorter telomeres, but interestingly, it did not demonstrate that depressive and anxiety disorders and LTL change together over time

Evidence-based pharmacotherapy in GAD

- Venlafaxine XR
- Escitalopram
- Paroxetine
- Pregabalin
- Sertraline
- Duloxetine
 - Benzodiazepines (short-term, not antidepressant)
 - Buspirone (antiaggressive, not antidepressant)
 - Imipramine (1 RCT)
 - Hydroxyzine (3 RCTs)

GAD treatment guidelines: WFSBP 2008





Effect size of medications for GAD

- Pregabalin 0.50
- Hydroxyzine 0.45
- Venlafaxine 0.42
- Benzodiazepines 0.38
- SSRIs 0.36
- *Buspirone* 0.17; not significant
- *Kava-kava, homeopathic preparation* 0.31; not significant

Comorbid GAD and insomnia

Adding eszopiclone to escitalopram treatment for 8 weeks resulted in a more rapid response and higher response rate.

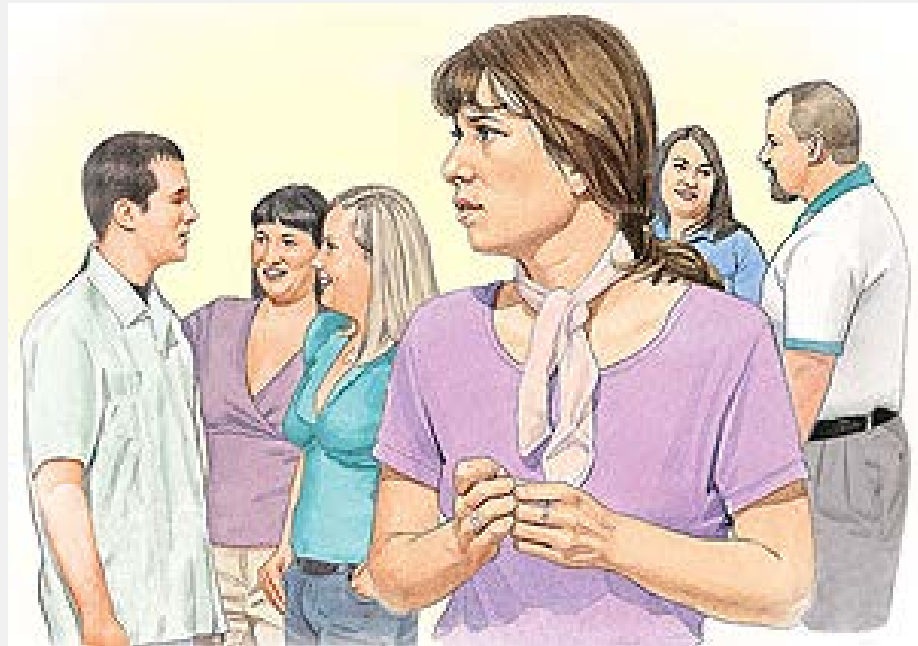
Effectiveness of CBT in GAD

CBT can be a highly effective treatment for reducing pathological worry, especially individual CBT in young patients.

Social Anxiety Disorder

Provoking situations

- Public speaking
 - Restaurants
 - Parties
 - Team work
 - Tests
 - Dating
 - Authorities
-



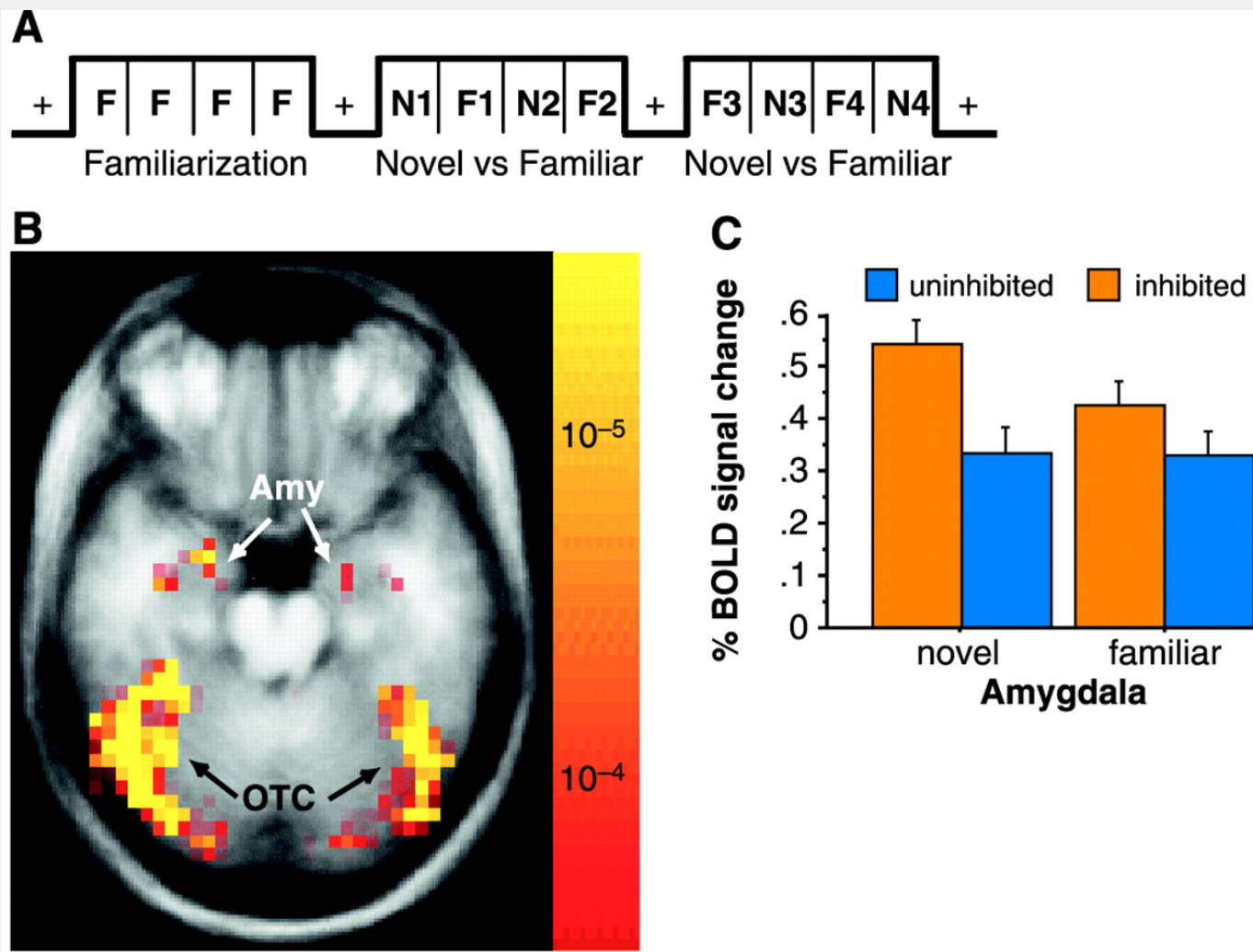


Naturalistic follow-up

Of 176 patients with social anxiety
only 36% were in remission after 8 years.

Amygdala Response to Novelty

Inhibited infants grown up



Guideline for treatment

- Patient education (booklet)
- Medications
 - beta-blocking agents (performance anxiety)
 - Paroxetine, escitalopram, fluvoxamine, sertraline
 - Venlafaxine
 - Clonazepam
- CBT, internet, self-help

Bandelow B et al. W J Biol Psychiatry 2008;9:248-312

Van Ameringen et al. Isr J Psychiatry Relat Sci 2009;46:53-61

Furmark et al. Br J Psychiatry 2009;195:440-47

Behavioural effects of treatment

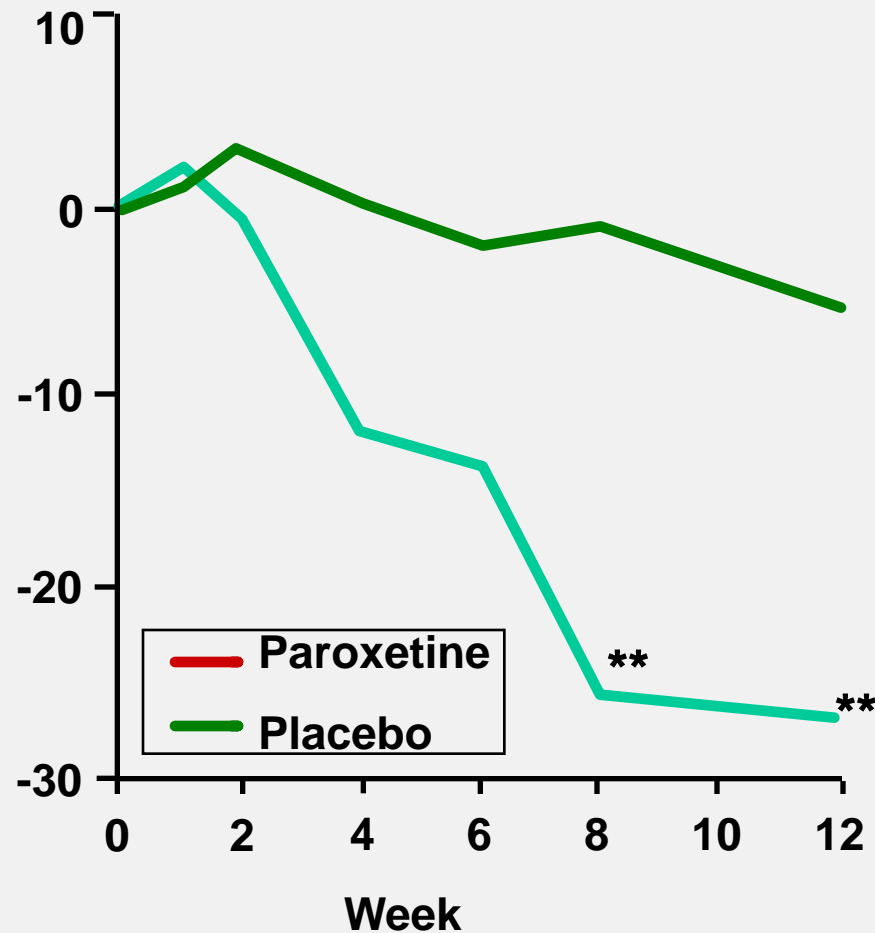
Patients with generalized anxiety on paroxetine and similar medications improved with regard to harm avoidance, cooperativeness, and self-directedness.

Study of 96 new patients with social anxiety disorder

- Advertisements for previously untreated cases in Stockholm
- Paroxetine 20-50 mg vs. placebo for 3 months
- Palm computer (Minidoc[®]) for LSAS, SDI, BSPS, FONE

Sheehan Disability Inventory: Work

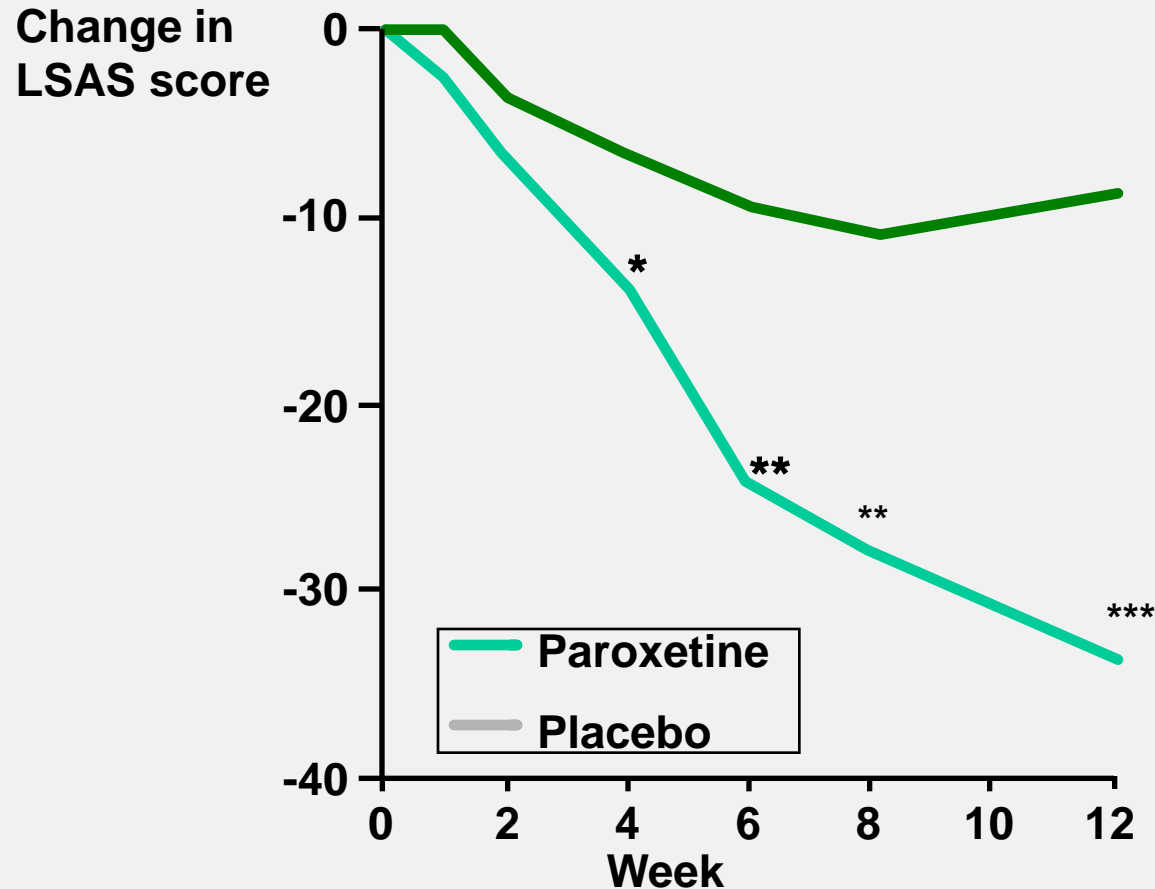
Change in
SDI score



** $p < 0.01$

Liebowitz Social Anxiety Scale

Total score

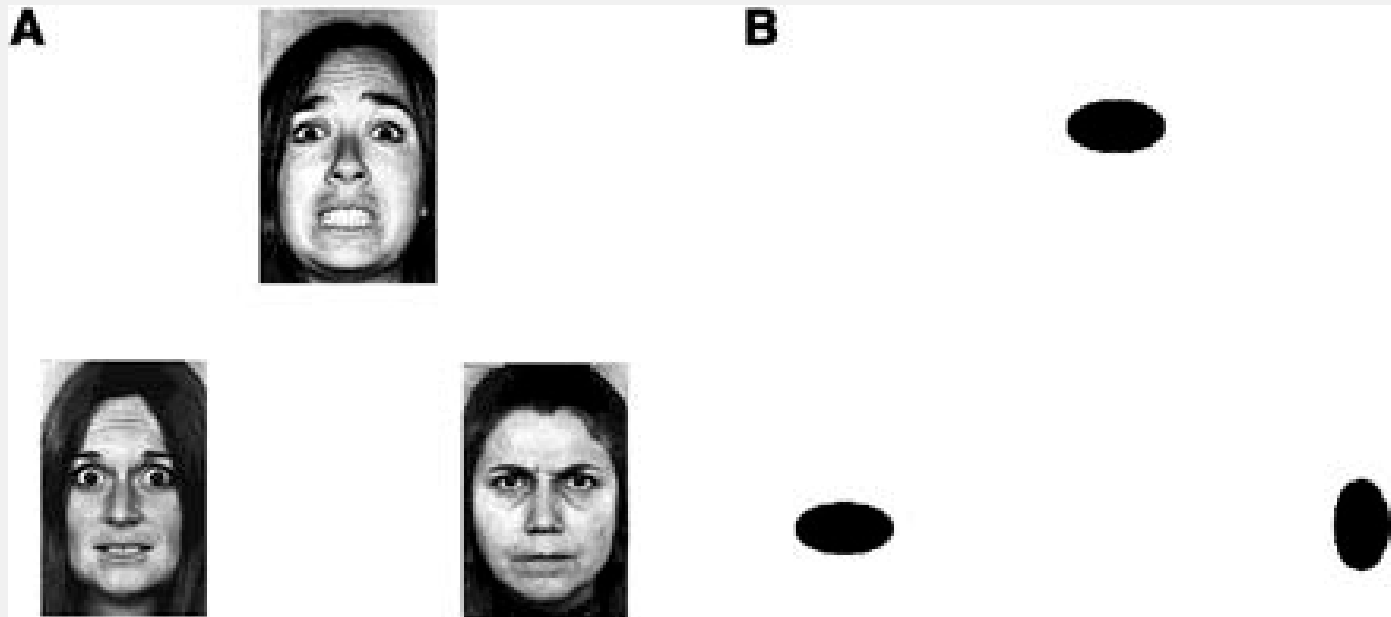


*p =0.052; **p<0.01; ***p<0.0001

Adverse events

	Paroxetine (n = 44) n	Placebo (n = 48) n
Discontinued due to ADRs	9	3
Sexual ADRs	18	4
Dose reduction due to ADRs	8	0
Discontinuation syndrome	6	0

Facial expression research





Acute SSRI improves the processing of social cues

24 healthy women were given 10 mg citalopram iv or saline. 30 minutes later the citalopram group detected fearful and happy faces more accurately and quickly.

Panic Disorder



Definition of panic disorder with agoraphobia

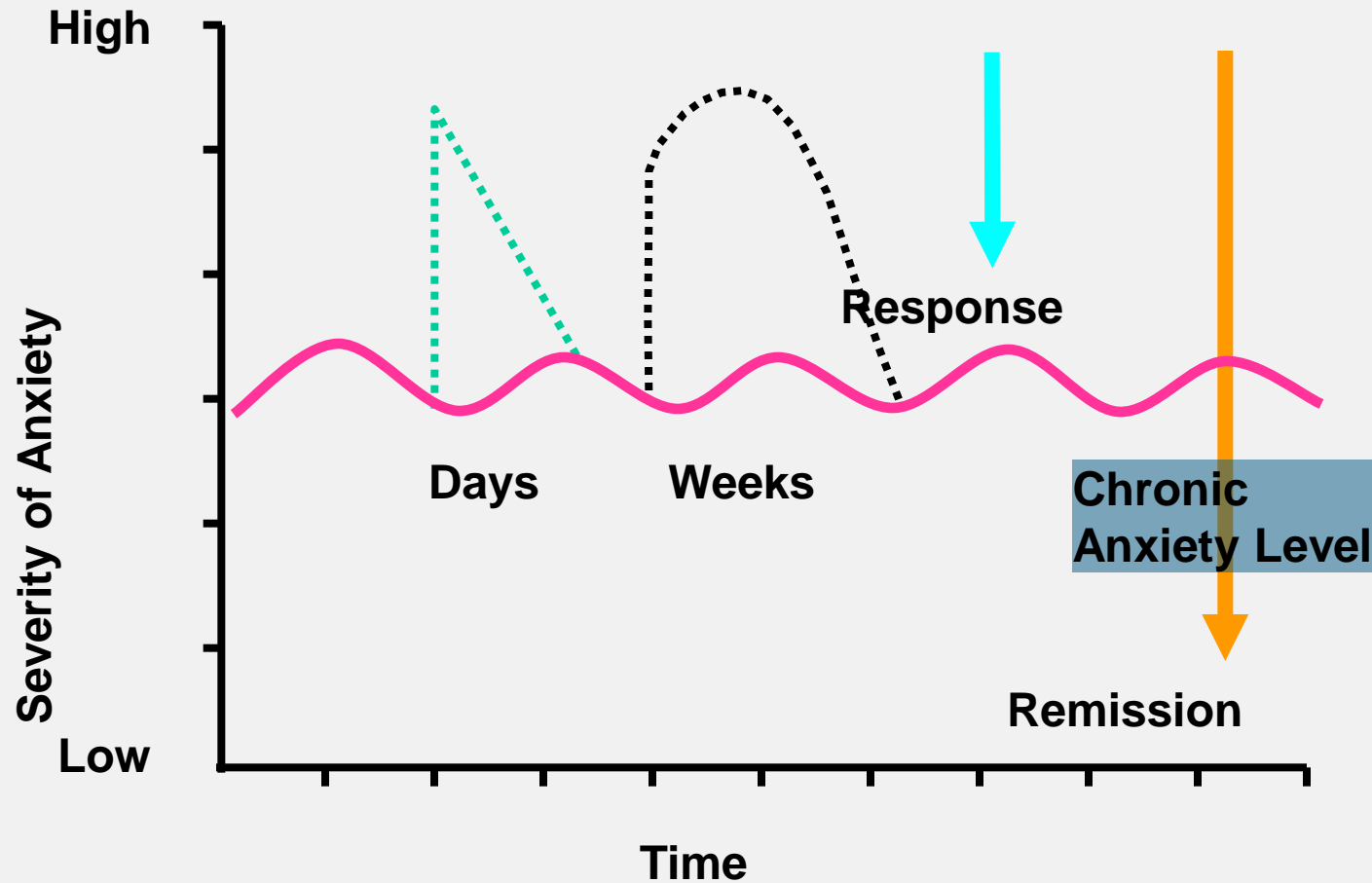
- “Recurrent unexpected panic attacks”
- “Persistent concern about having additional attacks”
- “Worry about the implications of the attack or its consequences”
- “A significant change in behavior related to the attacks”

Guideline for treatment

- Somatic check-up: ECG, TSH, T4.
 - Patient information
 - Medications
 - Paroxetine, escitalopram, sertraline
 - Venlafaxine
 - Alprazolam
 - CBT, internet, self-help
-

How to assess and monitor anxiety symptoms

Implications for Symptom Measurement





Hamilton Rating Scale for Anxiety

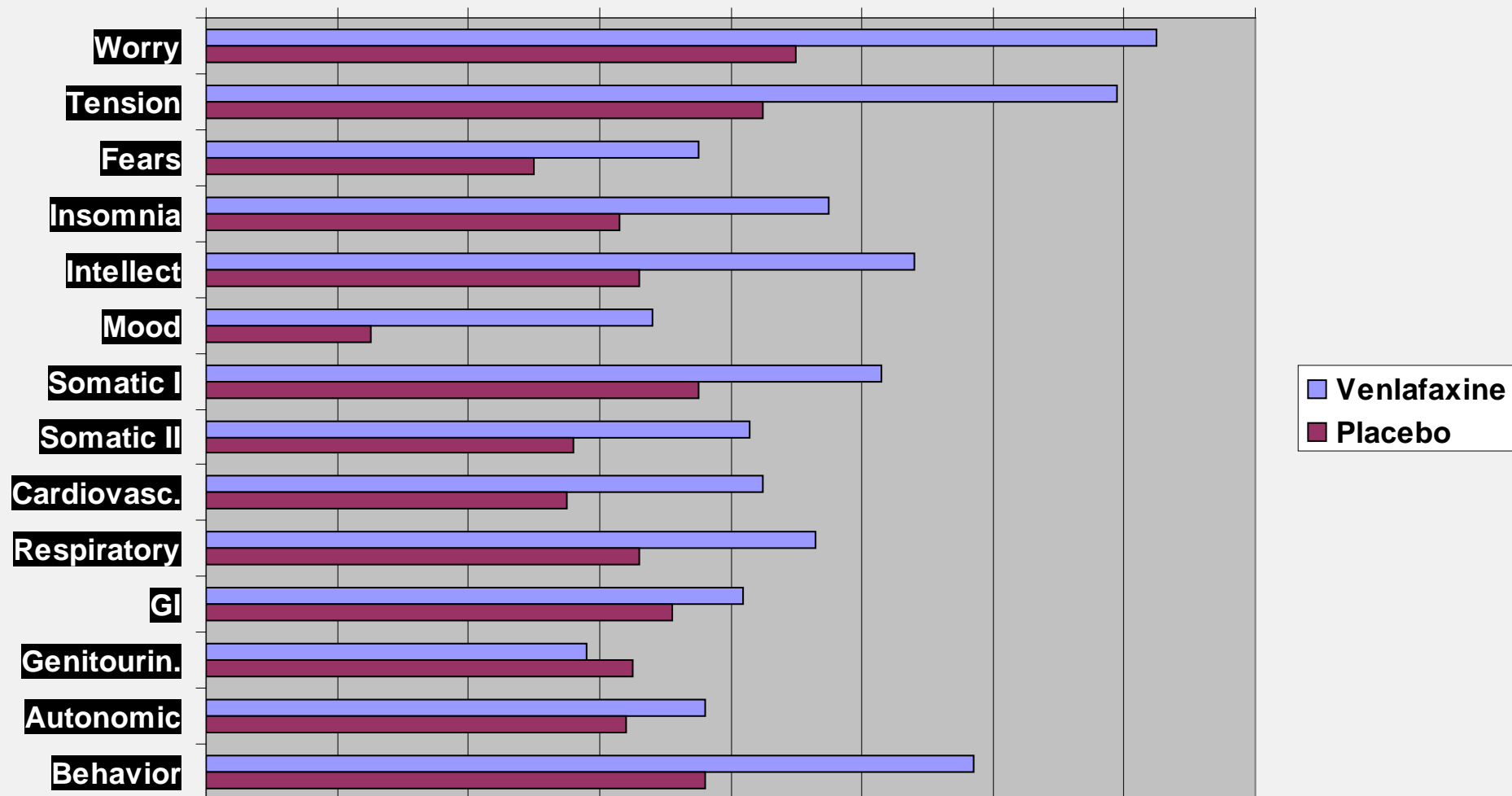
Item	Psychic	Somatic
1 Anxious mood	✓	
2 Tension	✓	
3 Fears	✓	
4 Insomnia	✓	
5 Intellectual (cognitive)	✓	
6 Depressed mood	✓	
7 Somatic (muscular)		✓
8 Somatic (sensory)		✓
9 Cardiovascular symptoms		✓
10 Respiratory symptoms		✓
11 Gastrointestinal symptoms		✓
12 Genitourinary symptoms		✓
13 Autonomic symptoms		✓
14 Behaviour at interview	✓	

HAM-A Scoring²
>25: Severe anxiety
19-25: Moderate anxiety
8-18: Mild anxiety



HAM-A Effect Size at 6 Months

0,0 0,2 0,4 0,6 0,8 1,0 1,2 1,4 1,6



Anxiolytics approved in Europe

	Panic disorder	GAD	Social anxiety
Paroxetine	X	X	X
Sertraline	X	X	X
Citalopram	X		
Escitalopram	X		X
Clomipramine	X		
Pregabalin		X	
Alprazolam	X		
Venlafaxine	X	X	X
Duloxetine		X	

Relapse prevention study in GAD

Escitalopram responders were randomized to continued escitalopram or placebo for up to 19 months.

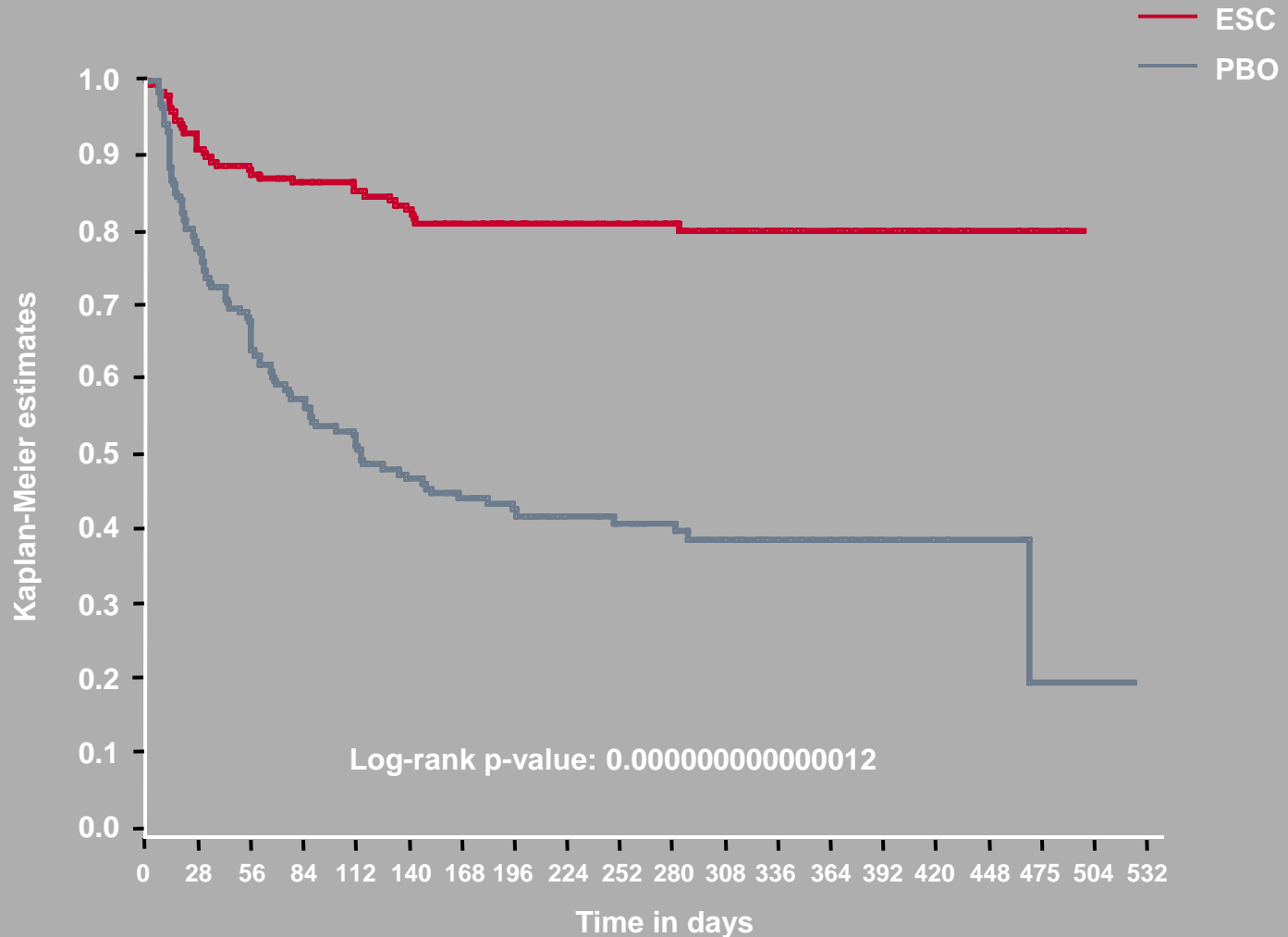


Time to relapse

ESC N=186 relapses: 35 (18.8%)

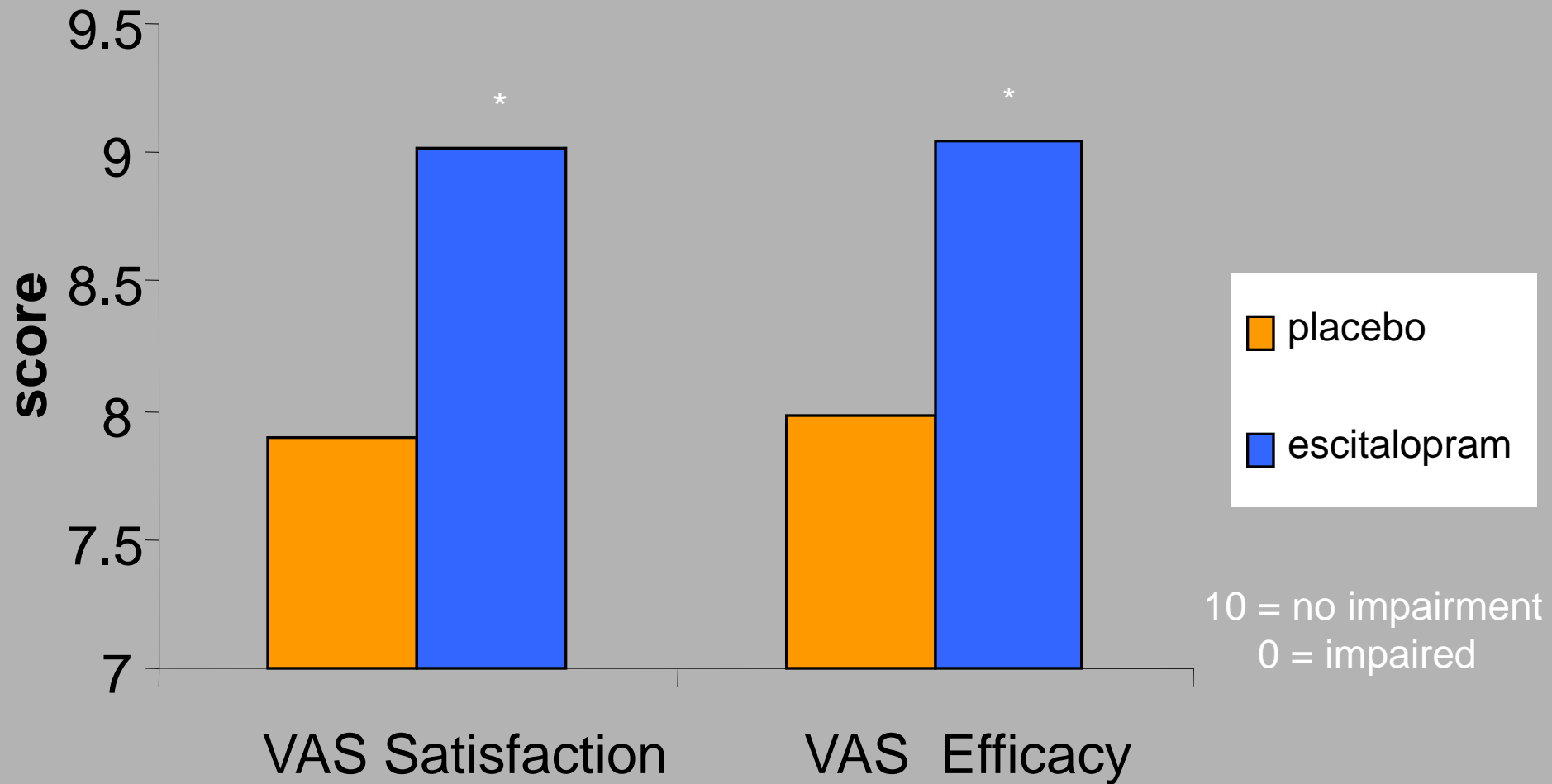
PBO N=187 relapses: 105 (56.1%)

Hazard ratio = 4.04





Work satisfaction and efficacy in GAD (LOCF)



* = $P < 0.005$

Allgulander C et al. Curr Med Res Opin 2007;23:2543-49

Anxiety in somatic diseases

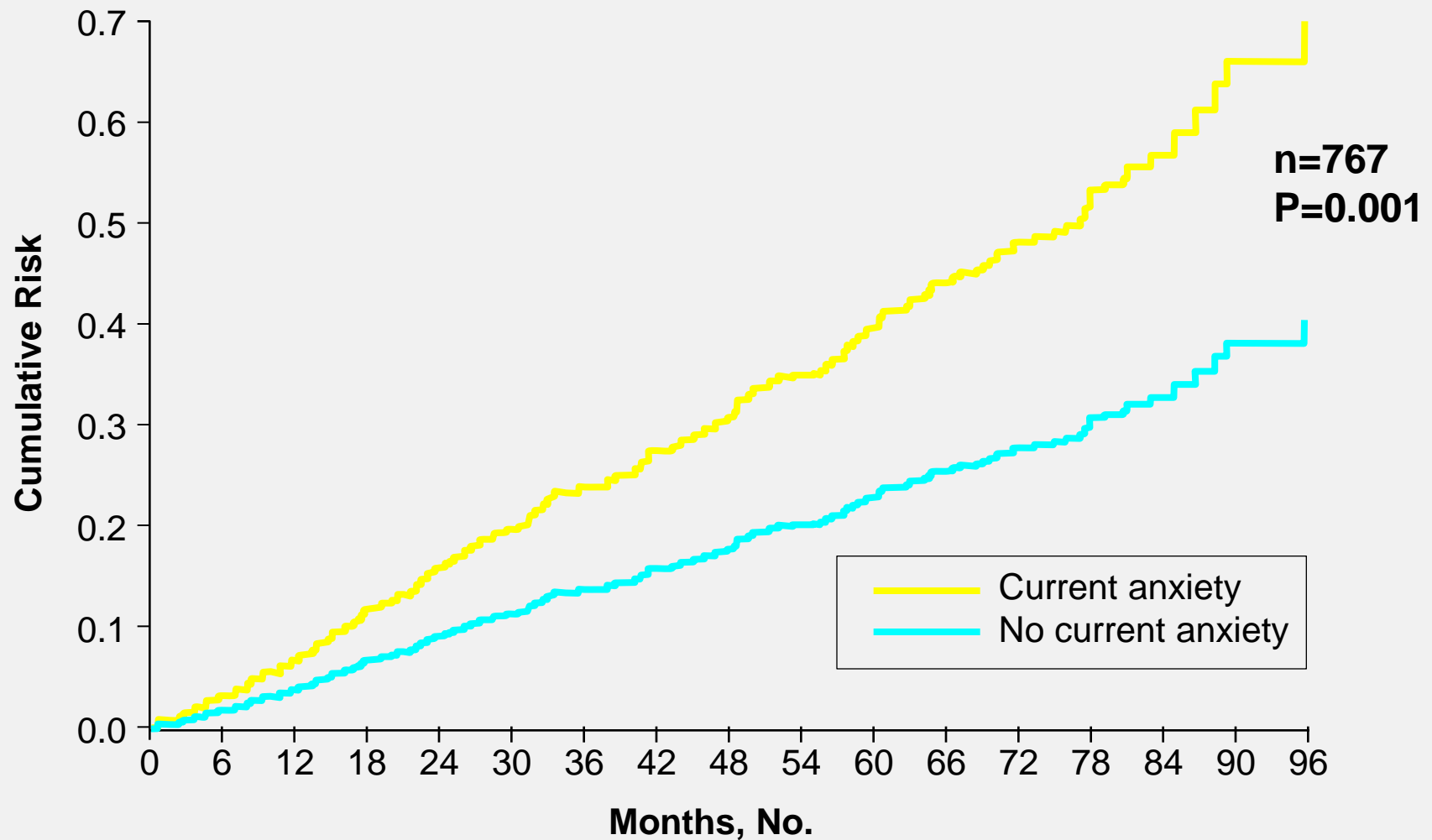
Narrative review: Anxiety in cardiovascular disease (CVD)

Anxiety apparently drives other known risk factors such as depression, obesity, tobacco smoking, diabetes, substance use.





Risk of cardiovascular events in stable CHD in the presence and absence of GAD

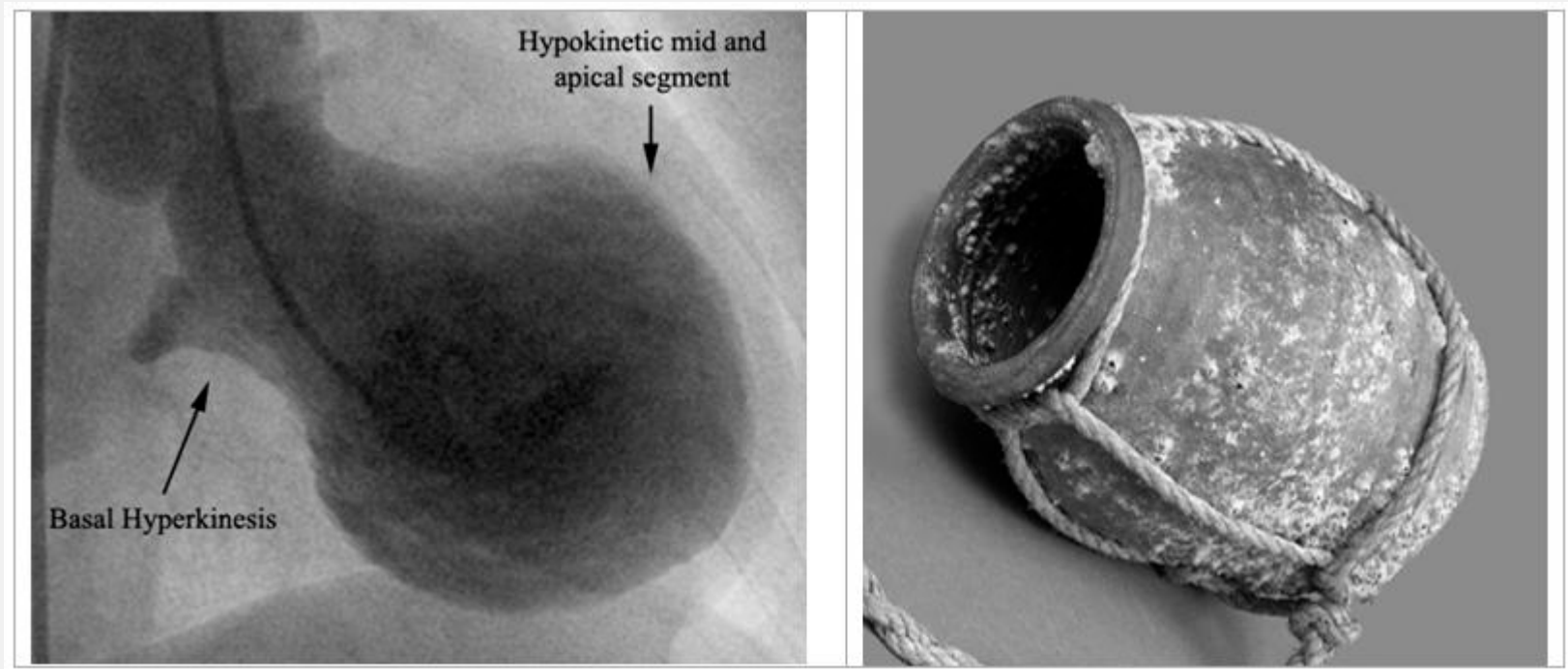




Association between symptoms of depression/anxiety and diabetes type 2

- A prospective population-based study in 37,291
 - 10 year follow up using questionnaire-based assessments
 - Anxiety and depression caseness based on the ADI
- Symptoms of depression and anxiety were significant risk factors for the onset of type 2 diabetes
 - No gender differences
 - No underlying factors that mediated the association were identified
 - Independent of established risk factors for diabetes, such as socioeconomic factors, lifestyle factors, and markers of the metabolic syndrome
- The comorbidity between depression and anxiety may be the most important factor
 - Comorbid anxiety might play a role in the increased activation of the HPA axis observed in patients with depression
- Diabetes did not predict subsequent symptoms of depression or anxiety

Takotsubo (broken heart syndrome)




White Coat Hypertension



Anna, 102 years old, healthy and witty





Psychiatric diagnoses among 85-year-olds in Göteborg without dementia

	Men n=104 procent	Women n=243 procent
Phobias	1	7
OCD	4	5
GAD/Panic	8	21
Depression	18	21
Psychosis	7	7
Hypochondriasis	0	2
Any of the above	29	37

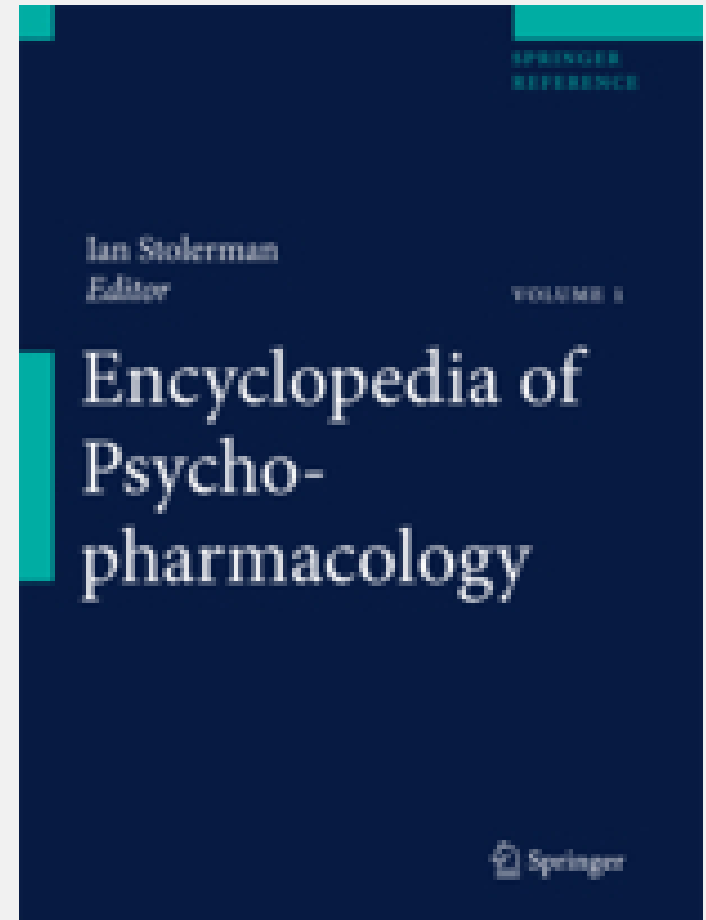
Ingmar Skoog dissertation 1993

Börjesson-Hanson et al. Am J Geriatr Psychiatry 2011;19:284-91

Benzodiazepine update

Christer Allgulander and
David Nutt:
Benzodiazepines

Springer, 2015
\$949



Benzodiazepines for these reasons

- Offer rapid anxiolytic effect
- Reinforcing only in predisposed substance abusers
- Have important clinical utility
- Are safe in overdose
- Are inexpensive

Benzodiazepine indications

- Insomnia
- Anxiety disorders (GAD, specific phobias, panic disorder, social anxiety disorder)
- Anxiety in depression (as an adjunct at initiation of antidepressant therapy)
- Schizophrenia (catatonic type, and for rapid tranquillization)
- Acute mania
- Organic brain syndrome (acute, e.g. delirium tremens, and chronic, e.g. dementia)
- Alcohol and sedative withdrawal
- Suicidal patients with prominent anxiety symptoms
- Adjustment disorders
- Avoidant personality disorder
- Status epilepticus
- Adjuvants in anaesthesia
- Tardive dyskinesia, akathisia
- Spasticity (e.g. spastic paraplegia), acute torticollis
- *Contraindications: Myasthenia gravis, sleep apnea, severe pulmonary disease*

Benzodiazepine memory effects

In a meta-analysis of tested subjects after a mean of 10 years of BZ treatment, significant impairment was found in all cognitive domains.

How to prescribe benzodiazepines

- Establish disabling anxiety/insomnia.
- Inform about reduced reaction time.
- Advise against concurrent alcohol intake.
- Use effective doses, regular or as needed.
- Monitor potential tolerance development.
- Ask for memory impairment, anterograde amnesia.
- Do not prescribe BZs to unreliable patients.
(Forging prescriptions, multiple prescribers, web).

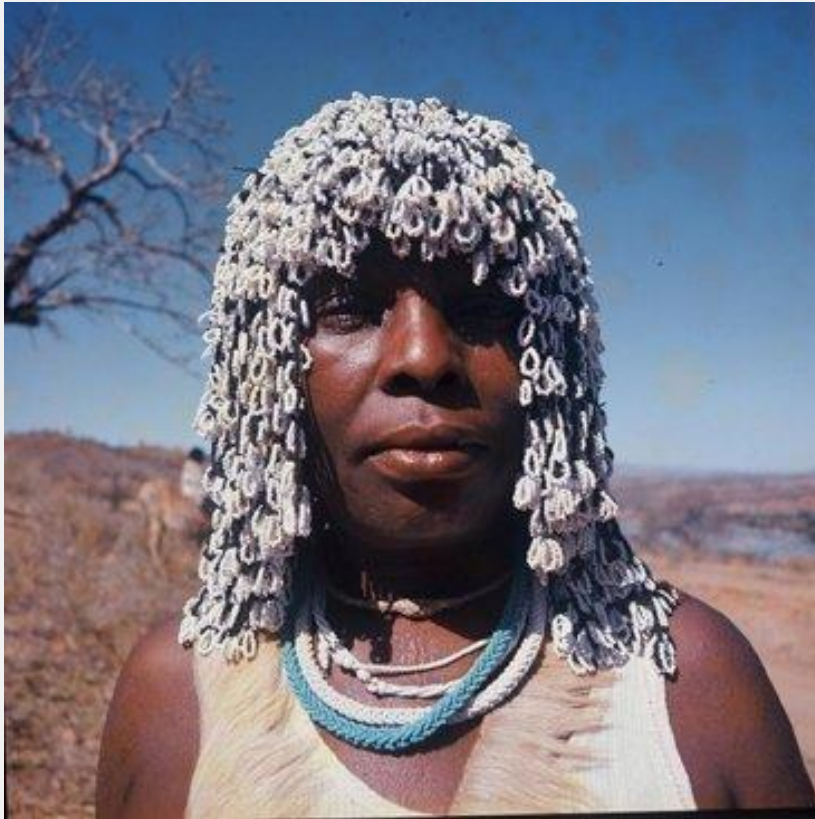
Adherence to pharmacotherapy



“All real helpfulness starts with humility regarding the person I want to help and because of this I must understand that helping is not to reign but to serve”

Søren Kirkegaard,
1813-1855

80% of the world population subscribe to traditional medicine (WHO)



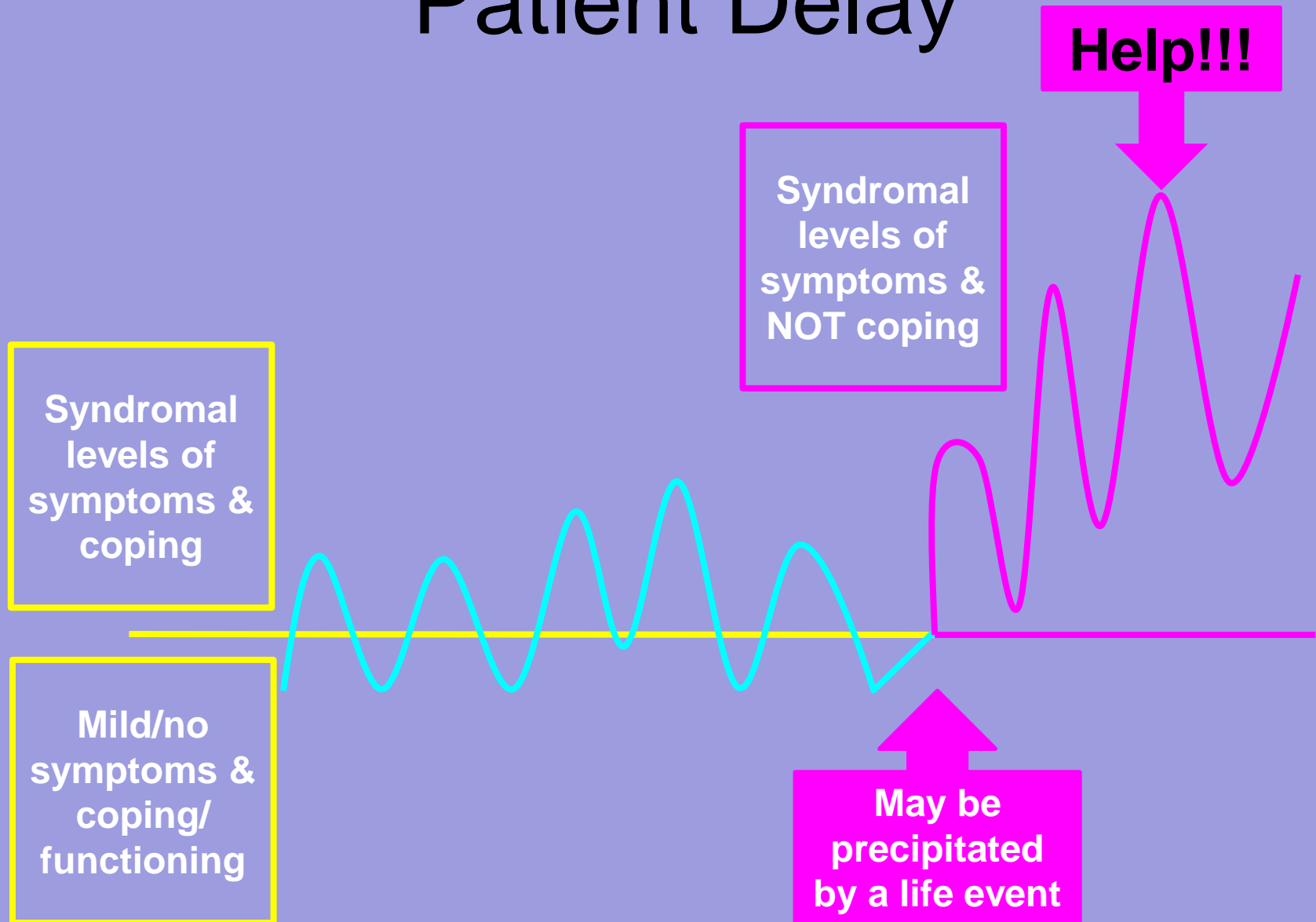
Incayawar M, Wintrob R, Bouchard L eds. Psychiatrists and Traditional Healers. Wiley-Blackwell 2009



Illness attribution and somatizing in Asian patients

- Shenjing shuairuo, wind overload, weak heart and weak kidney, neck soreness
- Hwa byung (catastrophic cognition)
- Neurasthenia

Patient Delay





Duration of GAD Before Treatment

100 outpatients with GAD in Mood Disorders Clinic in Milan¹

	Mean (SD) duration
Duration of GAD	12.8 (7) years
Before receiving treatment with benzodiazepines	58 (94) months
Before receiving treatment with antidepressants	84 (99) months

Getting the Patient on Board I

Not yet a patient:

- Stigma
- Illness attribution
- Cannot afford treatment

Getting the Patient on Board II

First visit diagnosed with GAD:

- Fear of addiction
- Worry about side effects (nocebo)
- Favors psychotherapy
- Internet expert (bibliotherapy)

Getting the Patient on Board III

While on successful treatment:

- Sexual side effects
- Weight gain
- Adherence
- How long do I continue treatment?

Attitude Survey in Sweden, 1987

People in general regarded antidepressants/anxiolytics to be as hazardous as alcohol, and more hazardous than cars and nuclear power



Fear of Addiction:

Defeat Depression Campaign, UK 1992

Most (78%) thought that antidepressants were addictive, and only 16% thought that they should be given to depressed people.

SUNUNU: Headed for a Fall?

TIME

SCIENTOLOGY

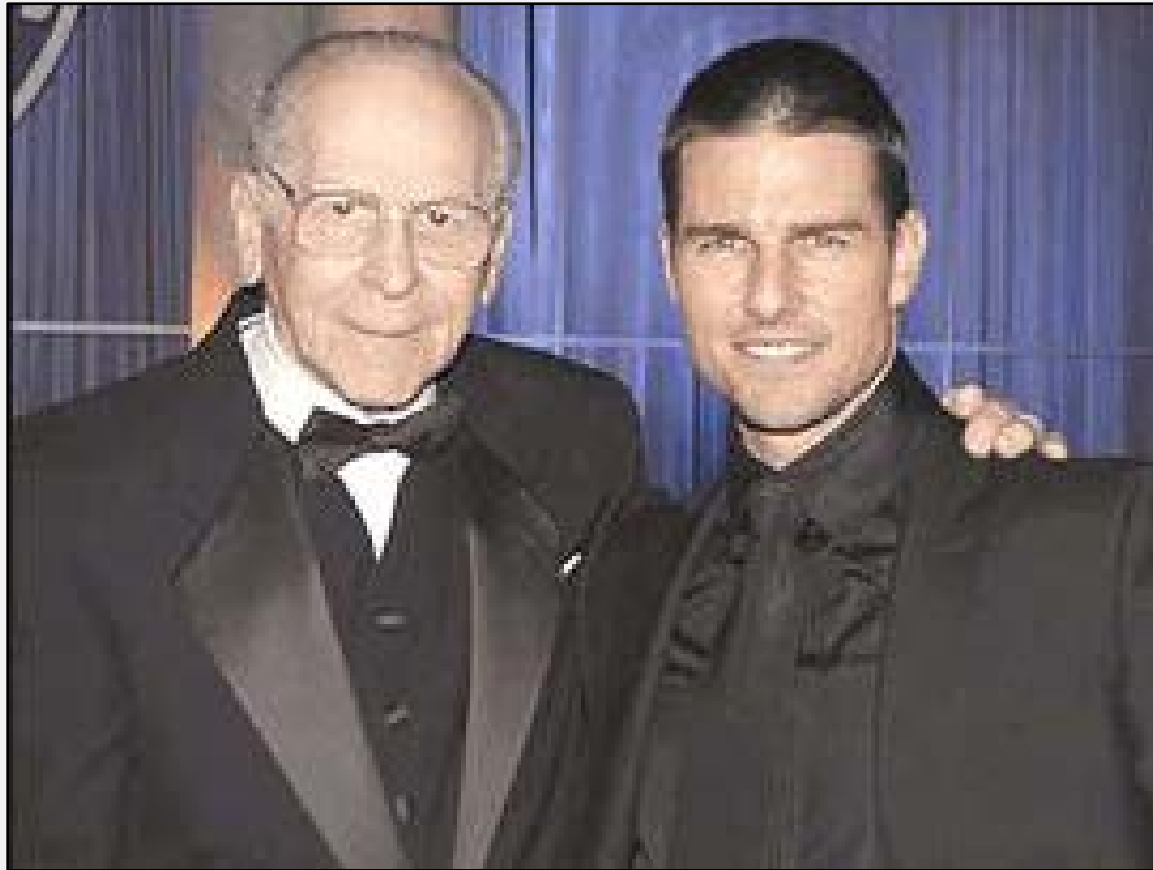
THE CULT OF GREED

HOW THE CHURCH OF
INDUSTRIAL EMPIRE
SOLD OVER 10 MILLION FROM
BELIEVERS WORLDWIDE

"THE KNOWING WOMAN THAT RECOGNIZES THAT PERSONS ARE INDIVIDUALS
 CAPABLE OF BEHAVIOR AT VARIOUS LEVELS OF RESPONSIBILITY
 DEMONSTRATES HER KNOWLEDGE AND CAPABILITY. THEREFORE," WWW.FORWOMEN.ORG

Foundations of a Theory of Personal Conduct

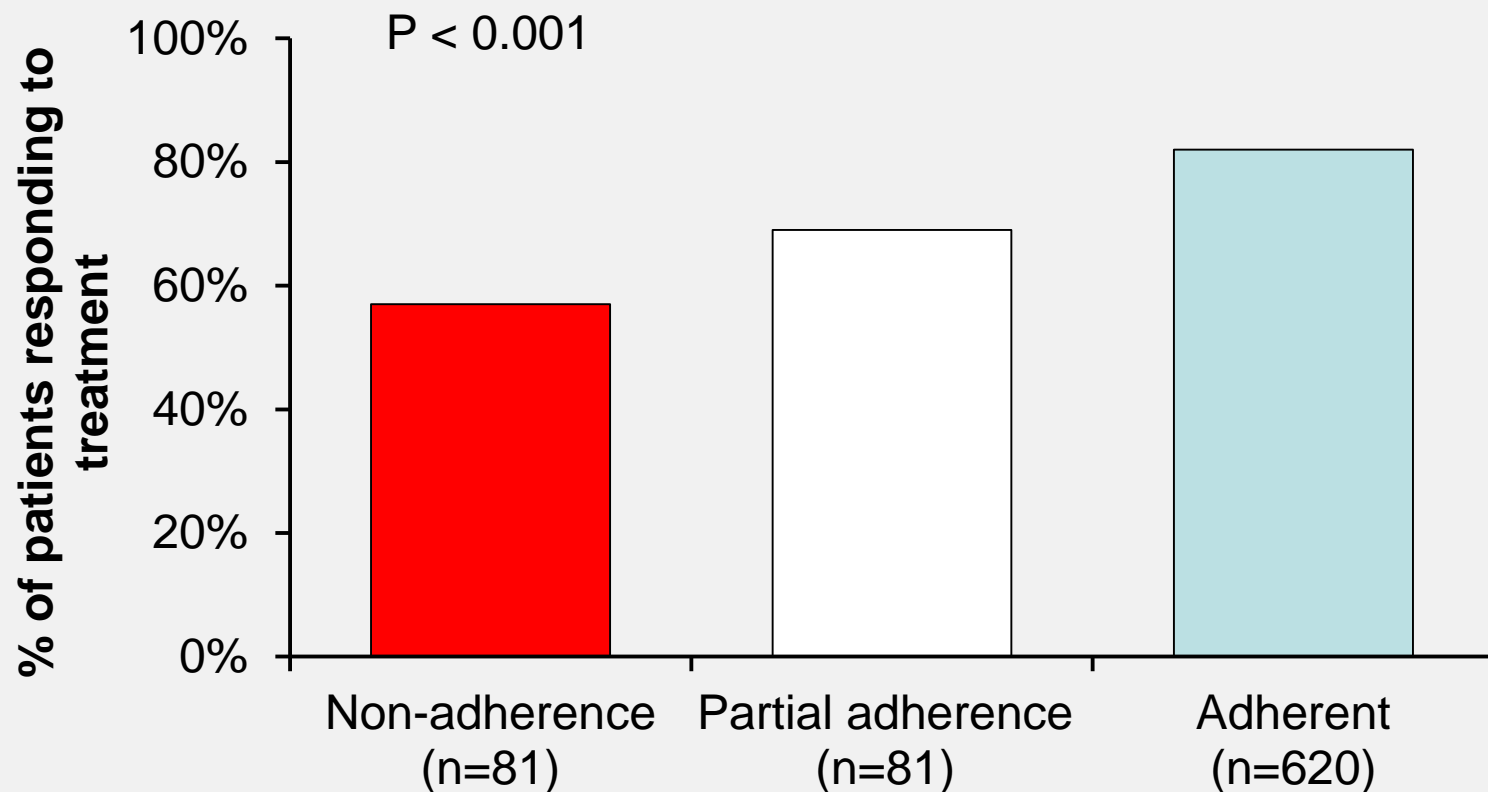
THOMAS S. SZASZ, M.D.



**Thomas Szasz and Tom Cruise
Hollywood, 2004**

Adherence and Outcome: Sertraline for Depression – Response Rate at 24 Weeks

Drug plasma assays taken in 792 primary care patients



Responder at week 24: MADRS $\geq 50\%$ reduction, CGI-Severity of normal to mildly ill,
and CGI-Improvement of much or very much improved

Reis et al. J Clin Psychopharmacol 2010;30:746-8



Tell the Patient Who Starts Treatment for GAD:

- Take medication daily
- Antidepressants/anxiolytics may take some weeks to work
- Continue taking medication even when feeling improved
- Do not stop taking medication without checking with the prescribing physician
- Inform about potential side effects
- Schedule pleasant activities

Addressing Addiction Concerns

Tell the patient that

- Many types of medicines cause withdrawal symptoms, such as antihypertensives and cortisone
- Addiction is craving for euphoria, getting high or sedated, not symptom amelioration
- Addiction is tolerance; a need to increase the dose
- Tolerance and craving do not exist with medicines approved for GAD

Anxiety may be a natural emotion!

