Treatment strategies of obsessive-compulsive disorder (OCD)

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Epidemiology of OCD

Prevalence	2 %
Sex	M=F
Age at onset	22-35 yrs
Civil status	50% single

Age of the first treatment	35-45 yrs

OCD

DIAGNOSIS

THERAPEUTIC PLAN

TREATMENT CHOICE

TREATMENT MANAGEMENT

DIAGNOSIS

DIAGNOSIS

- The OCD diagnosis is characterized by a great reliability
- Agreement between different observers and a more precise definition of syndromic boundaries
- The clinical diagnosis coincides with the presence of symptoms (obsessions and compulsions)
- Symptoms are well defined and easy to identify

DIAGNOSIS

- *Obsessions:* thoughts, images or impulses that recur and persist despite efforts to ignore or face them

- *Compulsions:* repetitive behaviors or mental acts that the person feels driven to perform in response to an obsession, directed at preventing or reducing distress or a dreaded event or situation

- *DSM 5, APA, 2016*

CLINICAL PICTURE

Characteristics of obsessions

Persistence

Recurrence

Intrusivity

Egodystonia

Resistance

Insight

Clinical Picture

Characteristics of compulsions

Ripetitivity

Coercition

Secondary to obsessions (not always)

Rigidity

Exaggeration

Clinical picture

Recurring *obsessions* and/or *compulsions* that

- are time consuming
- interfere with the activities of the subject
- are recognized as excessive or unreasonable

Common OC symptoms

- Contamination obsessions and washing rituals

- Doubt obsessions and checking rituals

- Symmetry, order, exacteness and precision obessions with related rituals

- Primary obsessive slowness

- Pure obsessions

Sex-related OCD symptoms

Men	obsessions	Sexual
		Accuracy and symmetry
Women	compulsions	Washing
		Cleaning

Differential diagnosis

Major Depressive disorder:	√ Ruminations, not obsessions √ Episodic course and development √ Later onset
Schizophrenia:	√ Stereotyped behaviors √ No resistance √ Conviction (no pathological doubt)
Tourette's disorder	√ Automatic symptoms √ Possible association (45-75%)

Differential diagnosis

Impulse control disorder	√ Pleasure is related to the activity, absent in a real compulsion
OC Personality	√ Presence of egosyntonia
Panic disorder	√ Specific symptoms √ Possible association (10%)

What should the patient know?

1. You are not alone. One out of 50 persons suffers from this disorder and most likely has very similar obsessions and compulsions
2. You are not crazy, and you should not be ashamed of being sick. You have to consider your obsessions and compulsions for what they are: the result of a disorder that goes beyond your control
3. Describe your symptoms to the psychiatrist that will consider them seriously, and will choose effective treatments
4. Be confident with the treatment although the results may initially be not encouraging. Several weeks are generally required before obtaining satisfactory results
5. Try to stay active and spend time outdoors. Confronting your fears and resisting your compulsions will help reduce the negative effects that the OCD has on your life

What can family and friends do to help the patient?

1. Do not blame the patient. OCD has nothing in common with weakness of character
2. Actively encourage the patient to consult a specialist
3. Never get involved in the obsessions and compulsions: this does nothing but strengthen them
4. Try to reduce the impact of OC behaviors by trying to have with the patient a normal relationship
5. Encourage each attempt of the patient, albeit small, to overcome his problem

Treatment options

- Pharmacotherapy
- Psychological therapy
- Other interventions

Bandelow B, et al. The World Journal of Biological Psychiatry 2008; 9(4):248-312

First - Line Treatments in OCD

A. Behaviour Therapy (Exposure + Response Prevention; 16 sessions; in vivo)

B. Pharmacotherapy (SSRIs *or clomipramine*; higher doses; extended duration - minimum 12 weeks)

Combination of A + B

However:

Up to 40% cases fail to respond (March et al 1997)

Better treatments are needed

PHARMACOTHERAPY

Consider:

- Symptom characteristics
- Level of individual adjustment
- Comorbidity

PHARMACOTHERAP

Therapeutic plan

Consider:

- Temperament / personality and personality disorders
- Longitudinal and current comorbidity
- Type of course
- Psychopharmacological history
- Level of insight
- Physical conditions

PHARMACOTHERAP

Therapeutic plan

Although OCD may have an episodic course, it is essentially a chronic disorder that requires prolonged treatment for long periods of time

Long periods of treatment are required even in the case of remission of symptoms after treatment

PHARMACOTHERAP

Therapeutic plan

Widely proven efficacy of pharmacotherapy

- Superiority over placebo of clomipramine and SSRIs demonstrated in controlled clinical trials

Fluvoxamine, fluoxetine, sertraline, paroxetine, citalopram, and clomipramine have therapeutic indications in OCD, according to inernational guidelines. Escitalopram is also effective

The pharmacological specificity of OCD

Effective

- Potent SRIs:
  - clomipramine
  - fluvoxamine
  - fluoxetine
  - sertraline
  - paroxetine
  - citalopram
  - escitalopram

Effective in combination with SRIs (unlicensed for OCD):

- 1st generation antipsychotics, e.g. haloperidol
- 2nd generation antipsychotics, e.g. risperidone, quetiapine, olanzapine

Ineffective

- *Tricyclics (apart from clomipramine)*
- *Monoamine oxidase inhibitors*
- *Lithium*
- *Benzodiazepines*
- *Buspirone*
- *Electroconvulsive therapy*

PHARMACOTHERAPY

Therapeutic plan

POSITIVE

Episodic course

Prevalence of obsessive symptoms

Later onset of symptoms

Shorter duration

Effectiveness of previous pharmacological treatments

PREDICTORS

NEGATIVE

Chronic course

Prevalence of compulsions

Earlier (childhood) onset of symptoms

Longer evolution

Inefficacy of previous specific pharmacological treatments

Lower insight

Personality Disorders Axis II, Schizotypal, OC, Borderline

PHARMACOTHERAP

Therapeutic plan

Significant psychometrical (Y-BOCS) and clinical improvement in 35-60% of treated cases

10% complete or almost regression of symptoms

High percentage of partial or total relapse related to discontinuation of pharmacotherapy

PHARMACOTHERAPY

Drug selection

Proven effectiveness

Tolerability of the specific active ingredient

Expected duration of the treatment

PHARMACOTHERAP

Drug selection

Medical conditions that may affect choice:

Previous pharmacological treatments of OCD

Severity of symptoms

Expected duration of the treatment

Psychiatric and physical comorbidity

PHARMACOTHERAPY

Drug selection

Only clomipramine and SSRIs have been proven to be effective in the treatment of OCD

Which SRI?

Controlled studies comparing SSRIs with clomipramine (CMI)

DRUG STUDY	n	DESIGN	OUTCOME Efficacy	 Tolerability
Fluoxetine (FLX) Piggott et al (1990)	11	CMI (50 -250mg) vs FLX (20 -80mg)	CMI=FLX	FLX > CMI
Lopez -Ibor et al (1996)	30 vs 24	CMI 150mg vs F LX 40mg	CMI=FLX on primary criterion CMI>FLX on other criteria	FLX = CMI
Fluvoxamine (FLV) Smeraldi et al (1992)	10	CMI 200mg vs FLV 200mg	CMI=FLV	FLV = CMI
Freeman et al (1994)	30 vs 34	CMI (150 -250mg) vs FLV (150 -250mg)	CMI=FLV	FLV > CMI (on se vere effects)
Koran et al (1996)	42 vs 37	CMI (100 -250mg) vs FLV (100 - 250mg)	CMI=FLV	FLV = CMI
Milanfranchi et al (1997)	13 vs 13	CMI (50 -300mg) vs FLV (50 -300mg)	CMI=FLV	FLV = CMI
Rouillon (1998)	105 vs 112	CMI (150 -300mg) vs FLV (150 - 300mg)	CMI=FLV	FLV > CMI.
Paroxetine (PAR) Zohar and Judge (1996)	99 vs 201 vs 99	CMI (50 -250mg) vs. PAR (20 -60mg) vs PLACEBO	CMI>PLACEBO PAR>PLACEBO	PAR > CMI
Sertraline (SER) Bisserbe et al (1997)	82 vs 86	CMI (50 -200mg) vs . SER (50 -200mg)	SER=CMI	SER > CMI
Citalopram (CIT) Pidrman & Tuma (1998)	24	CIT vs. CMI	CIT=CMI	CIT = CMI

Which doses?

Placebo-controlled comparator studies of fixed -doses of SSRI

DRUG STUDIES	FIXED DOSE	*n*	DURATION	Positive dose - response relationship?
Fluoxetine				
Montgomery et al (1993)	20/40/60mg	214	8weeks	YES [1]
Tollefson et al (1994)	20/40/60mg	355	13 weeks	NO
Sertraline				
Greist et al (1995)	50/100/200mg	324	12 weeks	NO
Paroxetine				
Hollander et al (2003)	20/40/60mg	348	12 weeks	YES
Citalopram				
Montgomery et al (2001)	20/40/60mg	352	12 weeks	YES [2]
Escitalopram				
Stein et al 2007	10/20mg	457	12 weeks	YES
			24 w eeks	YES

[1] marginally significant benefit for medium and higher doses on primary analysis (total Y-BOCS; $p = 0.059$); significant on 'responder' analysis ($p<0.05$).

[2] 60 mg significantly better than placebo and 20 mg on secondary analyses

PHARMACOTHERAPY

Clomipramine

First drug successfully used in OCD

Mean effective dose: 225 mg / day (range 100-300)

At these doses: marked adverse events, especially anticholinergic

Can be administered via IV, in case of drug resistance

Given the lower tolerability profile than SSRIs, the cost / benefit ratio should be closely evaluated, especially in case of long-term tretament

Fluvoxamine

First SSRI used in OCD

Higher potency than clomipranene on the SERT

Good tolerability up to 600 mg

Fluoxetine

First marketed SSRI for OCD

Mean potency of SERT inhibition

Range terapeutico tra 20 e 80 mg/die

Tolerability profile similar to that of other SSRIs

Paroxetine

SSRI with high SERT Potency inhibition

Therapeutic range between 20 and 80 mg/die

Better tolerability profile than clomipramine and similar to that of other SSRsS

Sertraline

SSRI with high SERT Potency inhibition

Therapeutic range between 50 and 200 mg/die

Tolerability profile similar to that of other SSRIs

Citalopram

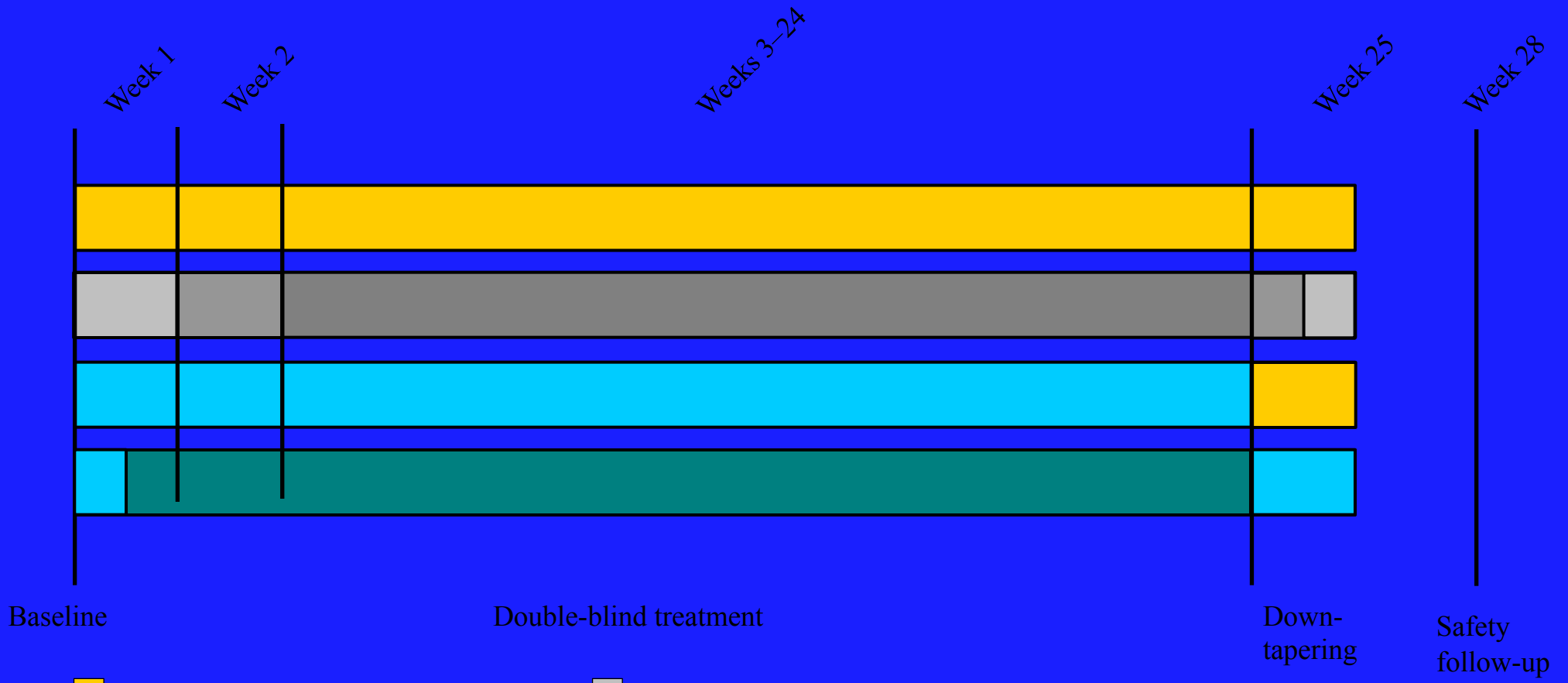
High SERT potency inhibition

Therapeutic range between 20 and 80 mg/die

Tolerability profile similar to that of other SSRIs

Is treatment effective in the long-term?

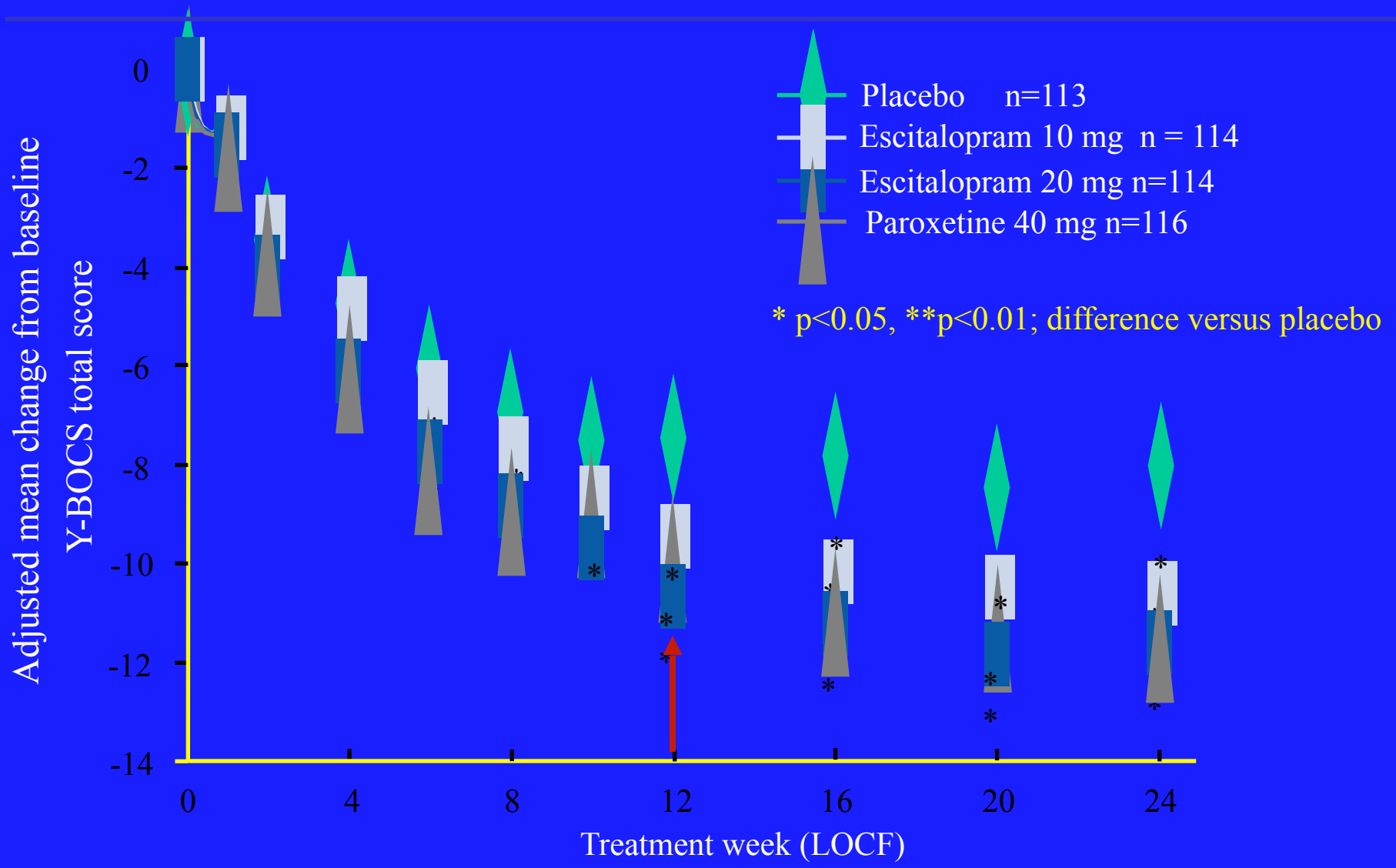
Escitalopram 10 mg, 20 mg vs paroxetine 40 mg and placebo: 24 weeks study



Stein et al. Poster presented at APA 2006

24 weeks fixed – dose escitalopram study: primary analysis

Stein DS et al. Curr. Med. Res. and Opinion 2007



Definitions of response, remission and resistance

Depend on dose and duration of treatment

Response = 35% improvement in YBOCS (? Full)
OR 25% (? Partial)
AND/OR CGI-I Score 1 or 2

Non-response = <25% improvement in Y-BOCS

(Pallanti et al 2002, Simpson et al 2006)

Remission = Y- BOCS $\leq$ 10

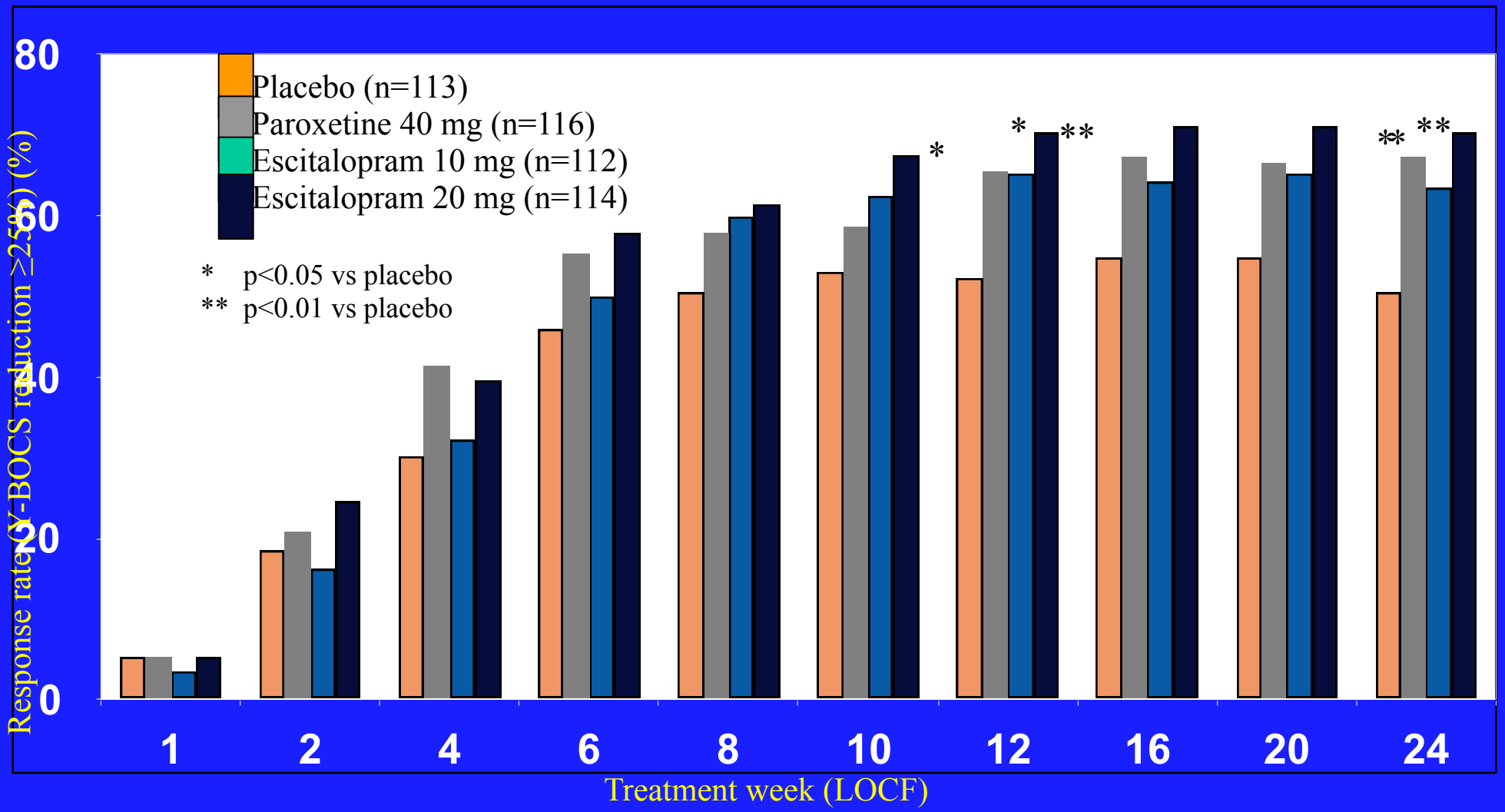
Standardised definitions of response could be refined using combined clinical databases, as for other anxiety disorders (Bandelow et al., 2006).
EG correlating Y-BOCS improvements with CGI-I scores

Treatment-resistance (SSRI resistance) = non- response to *two trials* of 12 weeks SRI at therapeutic dose

Treatment-refractoriness = failed *all available treatment*

Fineberg NA et al Int Clin Psychopharmacol. 2007 Nov;22(6):313-322

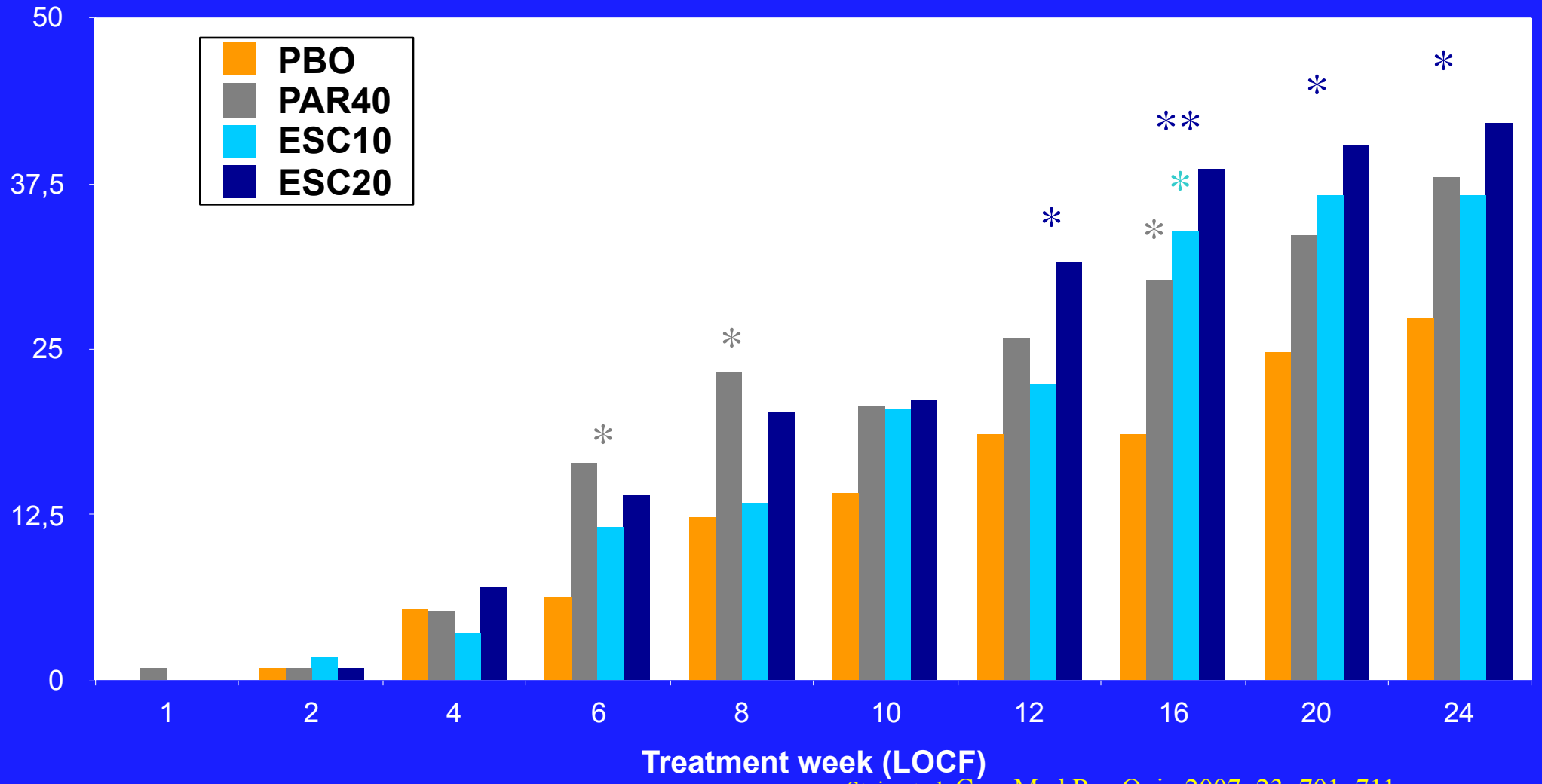
Escitalopram responders (≥25% reduction from baseline Y-BOCS)



Stein et al. Curr Med Res Opin 2007; 23: 701–711

Patients in remission (Y-BOCS ≤ 10)

Stein DS et al Curr. Med. Res. and Opinion 2007



Stein et al. Curr Med Res Opin 2007; 23: 701–711

* p<0.05 vs PBO, ** p<0.01 vs PBO

Does adding CBT improve outcomes?

Does adding CBT to SRI improve outcomes?
Randomised Studies

STUDY	DURN. (weeks)	OUTCOME	COMMENTS
Rachman et al (1979)	3	CMI+EXP = CMI+REL CMI+EXP = PLAC+EXP	OCscales No ITT
Marks et al (1980)	8	CMI+EXP > PLAC+EXP	Rituals & depression No ITT
Cottraux et al (1990)	24	FLV+EXP > PLAC+EXP	Rituals & depression No ITT
Hohagen et al (1998)	9	FLV+CBT > PLAC+CBT	Multimodal CBT
Foa et al (2005)	12	CMI + ERP > CMI > PLAC	No ERP control
Tenneij et al (2006)	52	SSRI+CBT > SSRI	12 wk SRI responders
Simpson et al (2008)	8	ERP+SSRI >stress mx+SSRI	After 12 wks SSRI; Y-BOCS >16.responder analys

Three controlled studies suggest adding SRI to CBT improves outcome over CBT given alone.

One controlled study suggests adding ERP to SSRI improves outcome over SSRI given alone (in partially resistant OCD).

How long to remain on treatment?

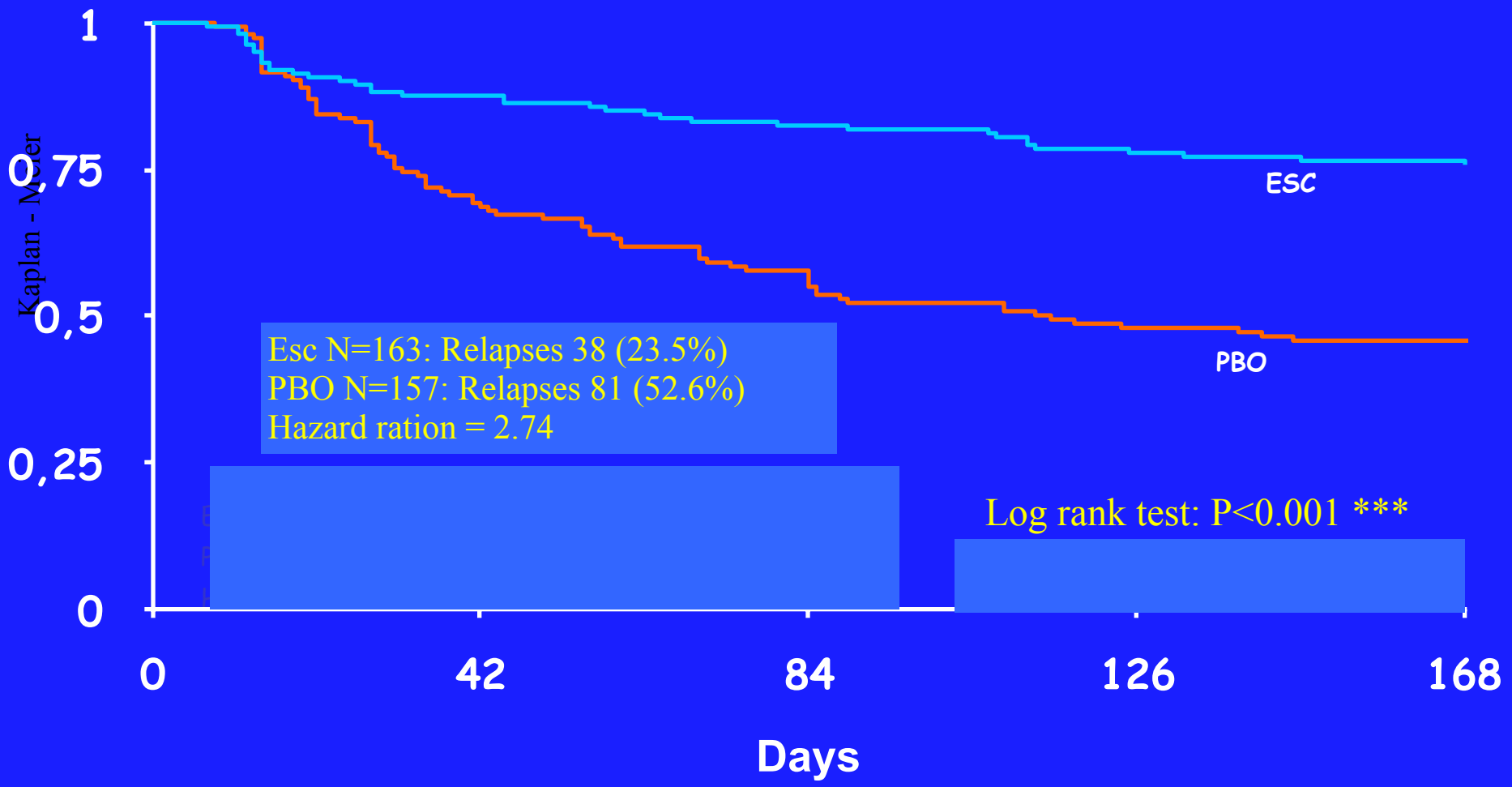
Double-blind studies of relapse prevention in OCD

STUDY	DRUG	Duration prior drug treatment	*n* in discont. phase	Follow - up after discont.	OUTCOME
Romano et al (1998)	fluoxetine	20 weeks	71	52 wks	Relapse rate on plac = pooled fluox Relapse rate on plac > f luox 60mg
Koran et al (2002)	sertraline	52 weeks	223	28 wks	Relapse rate on plac = sert Acute exacerb of OCD on plac > sert Dropout due to relapse on plac > sert
[b]Geller et al (2003)	paroxetine	16 weeks	193	16 wks	Relapse rate on plac = parox
Hollan der et al (2003)	paroxetine	12 weeks	105	36 wks	Relapse rate on plac > parox
Fineberg et al (2006)	escitalopra m	16 weeks	322	24 wks	Time to relapse on esc > plac Relapse rate on plac > esc

[b] in children and adolescents

How long to remain on treatment?

Esc vs placebo; time to relapse.

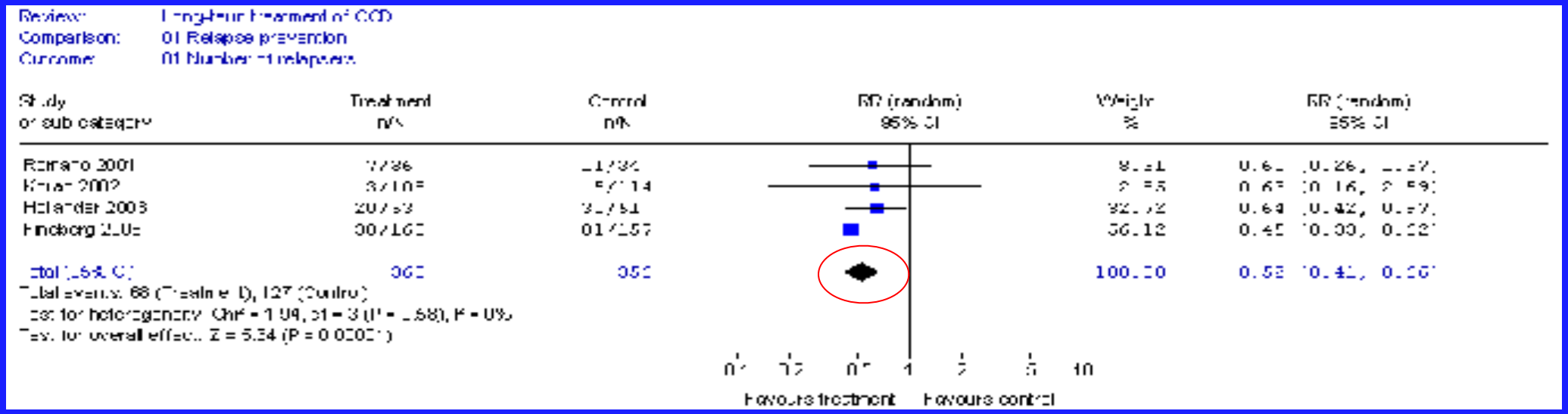


N=320 (ESC 163, PBO 157)

Fineberg et al. Eur Neuropsychopharmacol. 2007

Meta-analysis of SSRI (fluoxetine, sertraline, paroxetine, escitalopram) relapse prevention studies in adults with OCD

Fineberg et al Int Clin Psychopharmacol 2007



Sustained Response Versus Relapse: The Pharmacotherapeutic Goal For OCD.

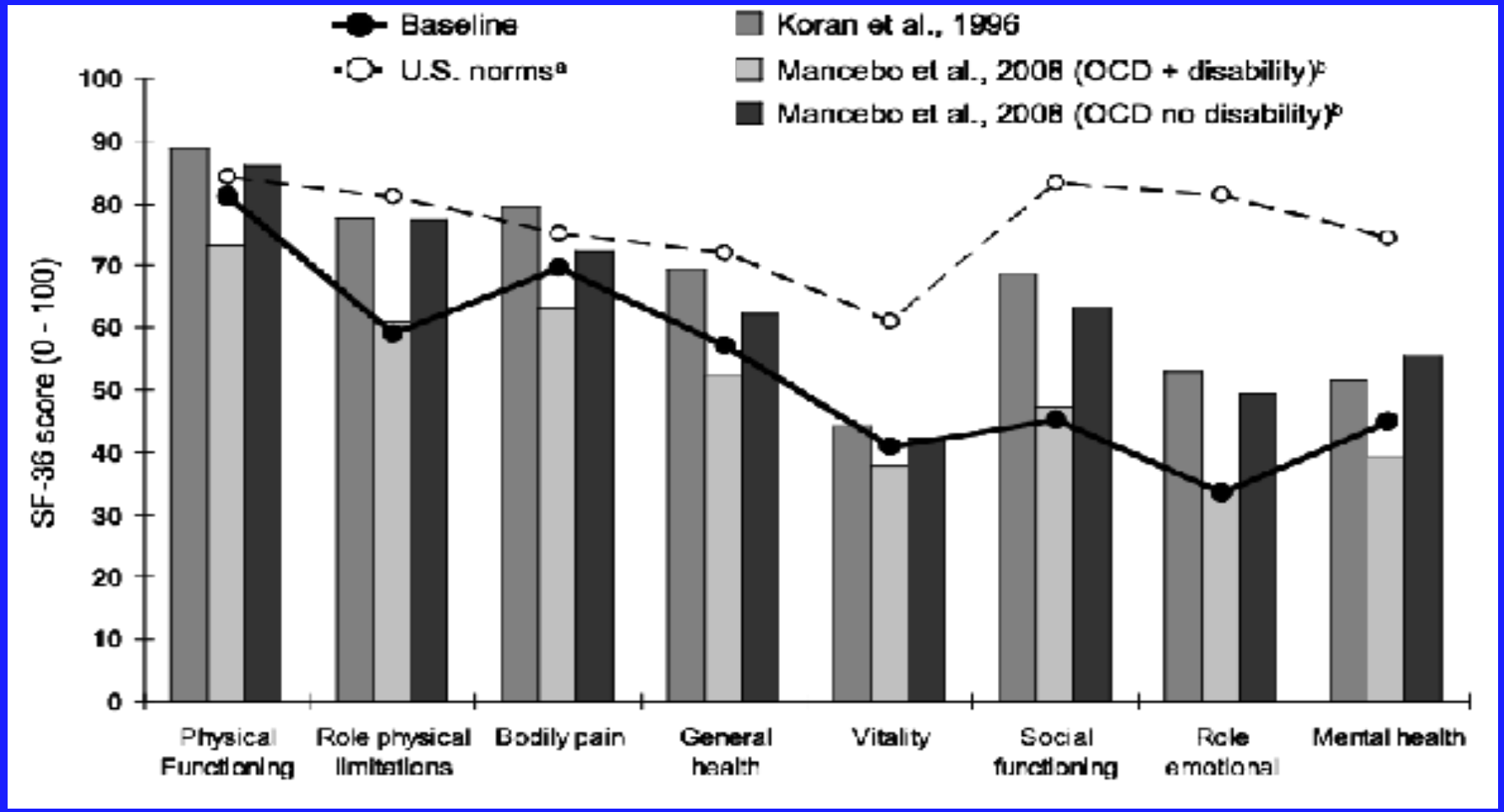
Fineberg NA et al Int Clin Psychopharmacol 2007

"OCD is a chronic disorder. On the basis of current evidence, long-term treatment with SSRIs is indicated to protect against relapse for most cases and treatment should not be discontinued.

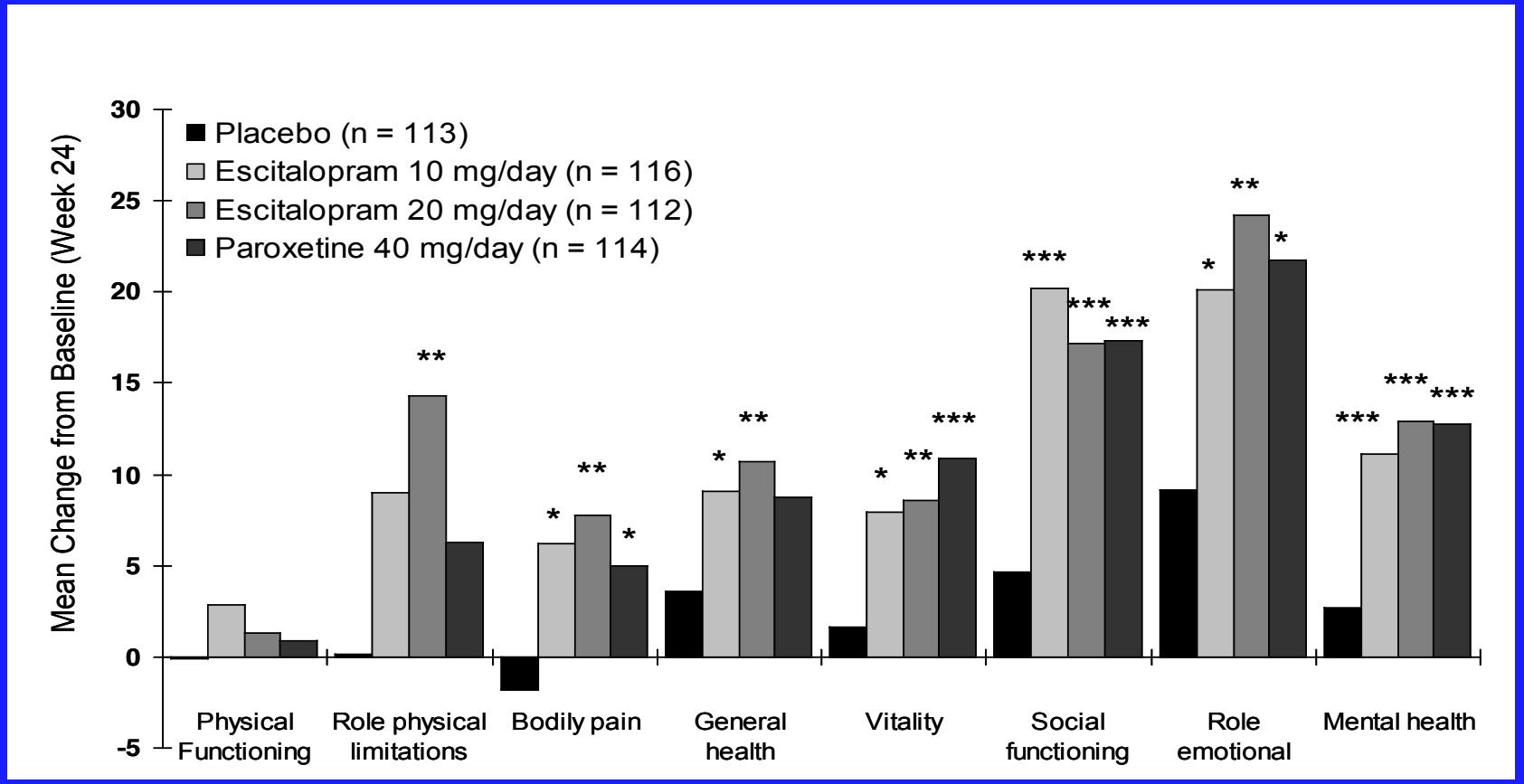
Clinicians need to inform their patients about the risks of relapse, so that collaborative decisions about maintenance treatment can be agreed."

Does SSRI improve health related disability and quality of life?

OCD; mean baseline SF-36 scores in combined escitalopram database (n = 921), compared to published U.S. norms and baseline data from two published studies of impact of OCD on SF-36 scores.

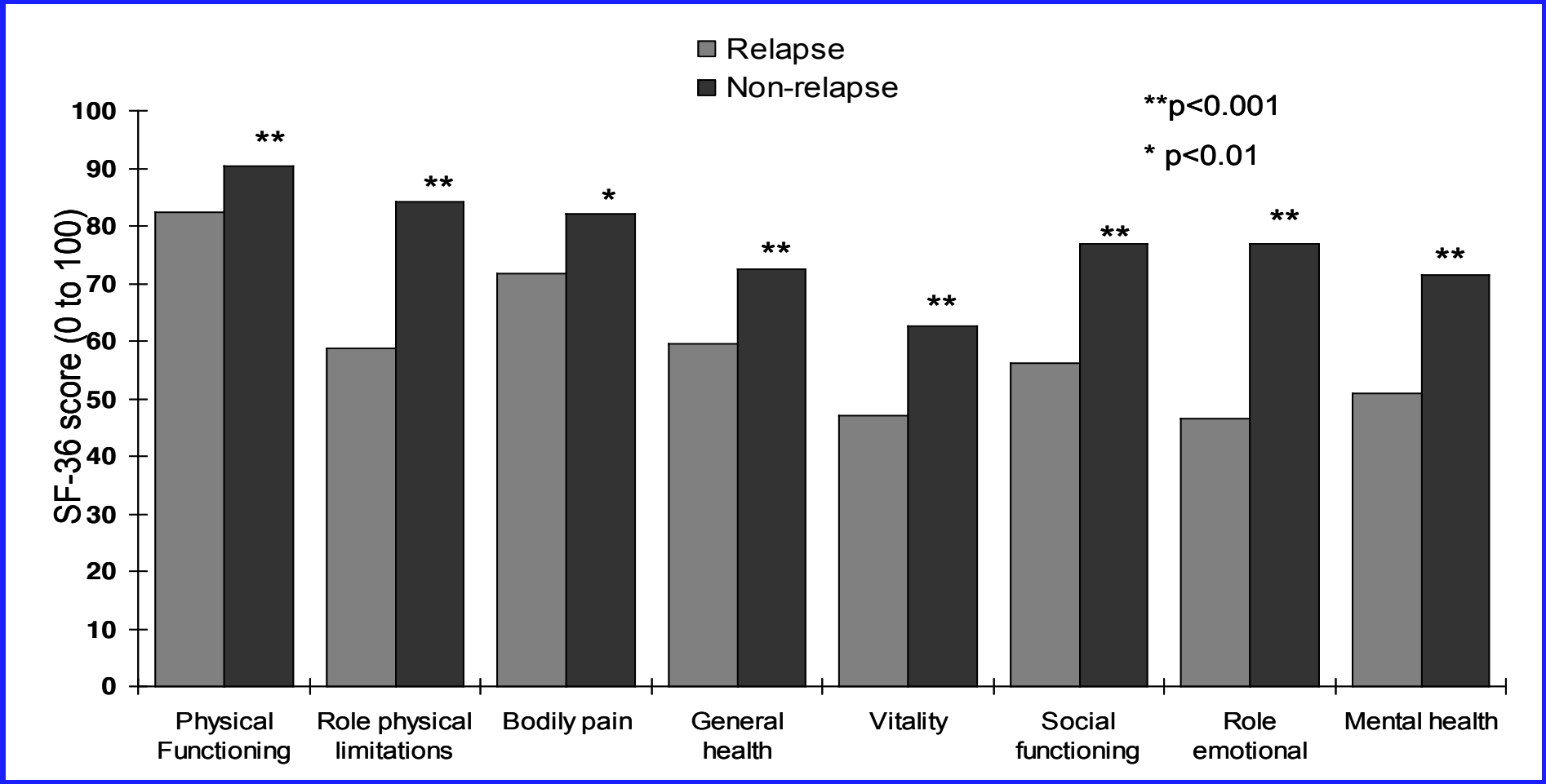


Mean change in SF-36 score from baseline to the end of 24 weeks in patients (n=455) receiving fixed-dose treatment with escitalopram, paroxetine, or placebo (FAS, LOCF)



*p<0.05, **p<0.01, ***p<0.001 vs. placebo (ANCOVA)

Mean SF-36 scores at last assessment for relapsed (n=119) and non-relapsed (n=201) patients (relapse-prevention study).



p<0.05, **p<0.01, ***p<0.001 vs. placebo (ANCOVA)

Symmetry/Hoarding predicts poor outcome to escitalopram

Stein D et al; CNS Spectr. 2008 Jun;13(6):492-8.

- 466 OCD patients in an 12 week RCT of escitalopram.
- Exploratory factor analysis of individual Y-BOCS items yielded 5 factors (contamination/cleaning, harm/checking, hoarding/symmetry, religious/sexual, and somatic/ hypochondriacal).
- Analyses of covariance for overall group demonstrated escitalopram more effective than placebo.
- A significant interaction for "hoarding/symmetry" was associated with a poorer treatment response ($p<0.001$).
- Hoarding/symmetry may characterise an early-onset group of OCD patients, with involvement of neurotransmitters other than serotonin.

Double-blind, randomised controlled studies in SRI-Resistant OCD

Appear effective:

- Adding haloperidol[b]
- Adding risperidone
- Adding quetiapine
- Adding olanzapine
- High dose SSRI
- Intravenous clomipramine[a]

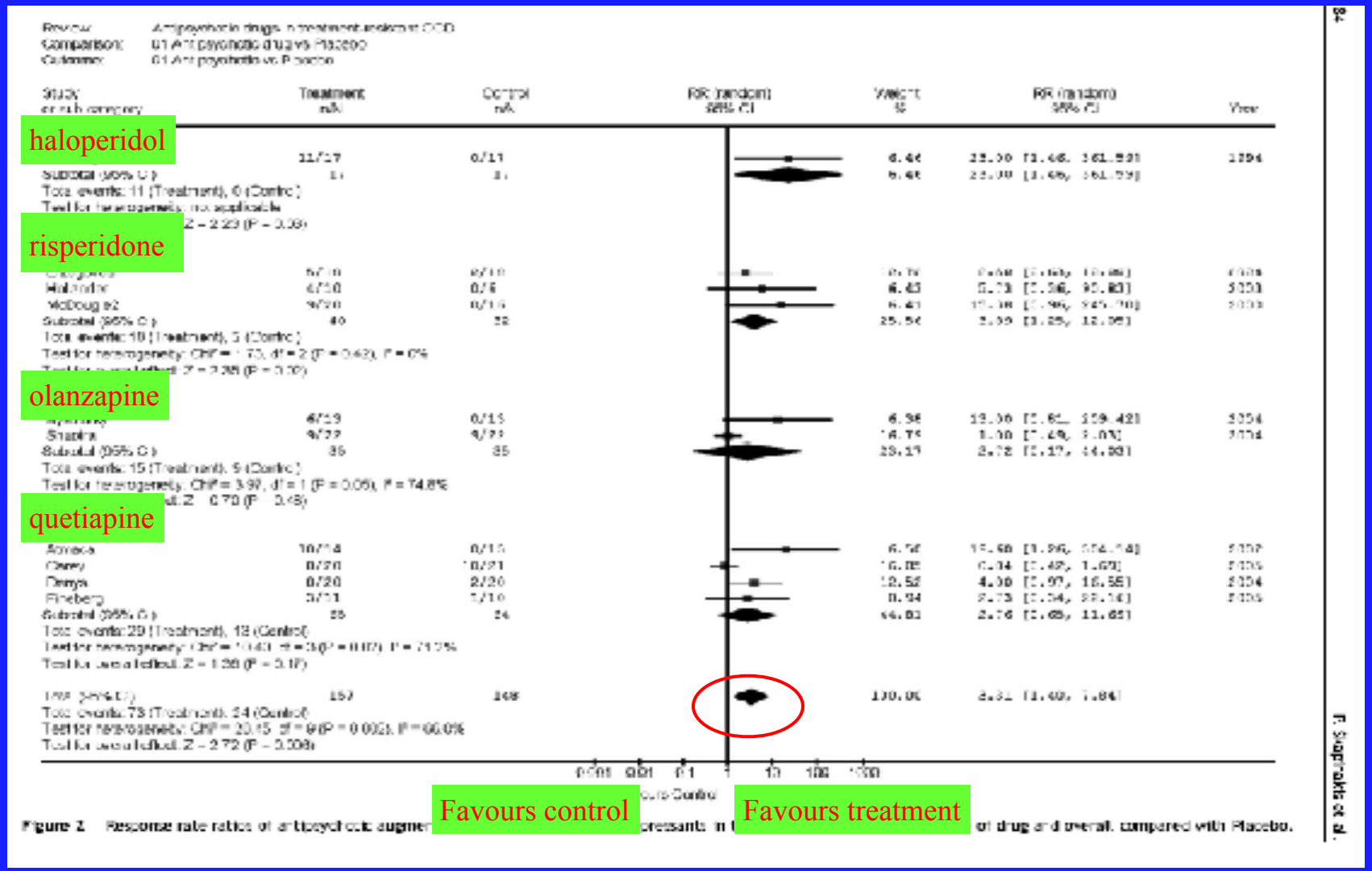
} ? Class 1

Apparently ineffective:

- Adding lithium
- Adding buspirone
- Adding triiodothyronine (liothyronine)
- Adding desipramine
- Adding inositol
- Adding clonazepam
- Adding naltrexone
- Adding oxytocin

a. Remains investigational in many countries
b. Primarily in 'tic-related' OCD

Antipsychotic augmentation of SRIs in resistant OCD



Skapinakis P et al. Eur Neuropsychopharmacol 2007; 17: 79-93

Higher-dose SSRI monotherapy for resistant OCD?

Ninan et al J Clin Psych 2006

- 66 OCD non-responders to 16 weeks of sertraline, randomly assigned:
- 12 weeks high-dose sertraline (250-400 mg/day, mean = 357mg, N = 30) showed significantly greater improvement than 200mg/day (N = 36) on YBOCS, NIMH Global OC Scale, CGI-I.
- Responder rates not significantly different between groups, either on completer analysis (52 % vs. 34 %) or endpoint analysis (40 % vs. 33 %).
- Both treatments showed similar adverse event rates.
- Conclusion: Higher than labelled SSRI doses may be a treatment option for OCD patients who fail to respond to standard treatment.

SRI	Usual Max Dose (mg/day)	Occasionally Prescribed Max Dose (mg/day)
citalopram	80	120
clomipramine	250	-
escitalopram	40	60
fluoxetine	80	120
fluvoxamine	300	450
paroxetine	60	100
sertraline	200	400

American Psychiatric Association. (2007).Practice guideline for the treatment of patients with obsessive-compulsive disorder. Arlington (VA): Koran L et al; American Psychiatric Association (APA); 96 p.

Supra-formulary dosing of SSRIs in OCD: a systematic review

- 26 (13.5%) of the clinic received high-dose SRI for 3–364 wks (mean 81.5 wks) over which period sig. within-group improvements were made (Y-BOCS baseline 25.4 vs endpoint 21.0)
- *Endpoint scores* for the high-dose group remained sig. higher than controls treated for a matched period (Y-BOCS 21.0 vs. 15.5), suggesting they possessed enduring treatment-resistance.
- Frequency of AEs (@50%) did not sig. differ between high and non-high dosed groups. Severe AE (fit) observed in one case with ASD.
- Sustained high-dose SRI was associated with clinical improvement and was well-tolerated in a particularly refractory OCD sample.
- AE monitoring advisable, with special care in comorbid cases.

Intravenous SSRI / clomipramine

- Pulse loading with IV (but not oral) clomipramine produced an early and rapid decrease in symptoms but the advantage was not sustained (Koran et al 1997)
- Two double blind RCTs supported the efficacy of IV clomipramine in resistant OCD (Fallon et al 1998; Koran et al 1997)
- An open label study of IV citalopram hinted at efficacy (Pallanti et al 2002)

PHARMACOTHERAPY

Treatment management

ACUTE PHASE

All patients

STABILIZATION PHASE

6 months
dose piena

All patients

MAINTAINANCE PHASE
2-3 years
dose ridotta (metà)

Response

SLOW DRUG DECREASE
in two years

STOPPING PHARMACOLOGICAL TREATMENTS

No response

CONTNUE TREATMENT, SOMETIME FOR EVER

PHARMACOTERAPIY

In the long-term treatment

CHECK:

- WEIGHT GAIN
- SEXUAL DYSFUNCTIONS
- APATHY OR DISINHIBITION

PHARMACOTHERAPY

ALGORITHM

DIAGNOSIS

SSRI OR CBT

NO RESPONSE:
Check doses and duration

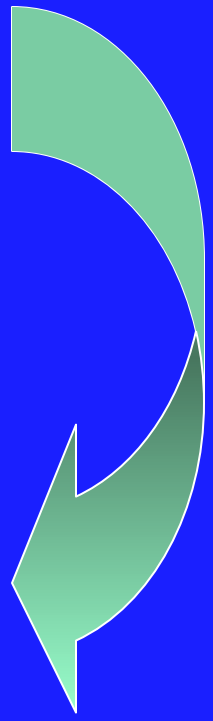
Try other SSRIS OR
CMI)

NO RESPONSE

ASSOCIATION AND AUGMENTATION
STRATEGIES

NO RESPONSE

OTHER TREATEMENTS



CMI o
Cital
IO.v.

PHARMACOTHERAPY

NO RESPONSE

EVALUATE:

A) SUBTYPES OF OCD
B) TRIGGER SYMPTOMS

PHARMACOTHERAPY

NO RESPONSE

A) SUBTYPES OF OCD

1. Harm avoidant
2. Simmetry, “Just so”
3. Low insight
4. Neurological subtype
5. Primary obsessive slowness
6. PANDAS

PHARMACOTHERAPY

NO RESPONSE

Trigger symptoms

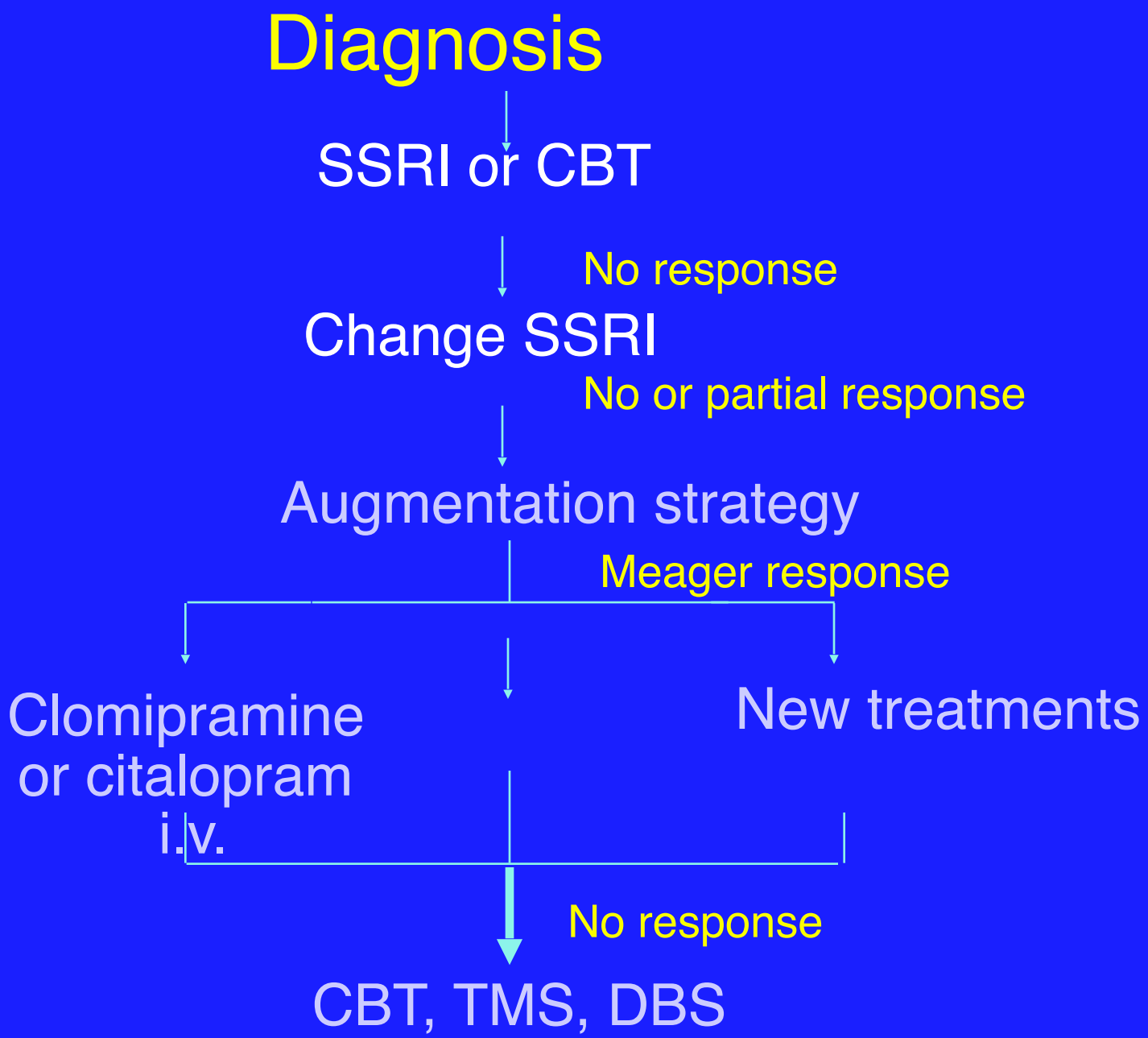
1. Anxiety
2. Depression
3. Delusions
4. Neurological symptoms and EEC abnormalities
5. Agitazion, ADHD, impulse control disorders
6. tics

PHARMACOTHERAPY

NO RESPONSE

EVALUATE:

- Comorbidity with anxiety disorders
- Comorbidity with bipolar spectrum disorders
- Comorbidity with schizophrenia and psychotic disorder
- Medical comorbidities


Diagnosis
SSRI or CBT
No response
Change SSRI
No or partial response
Augmentation strategy
Meager response
Clomipramine
or citalopram
i.v.
New treatments
No response
CBT, TMS, DBS

Common mistakes in OCD treatment

- Misdiagnosis
- Insufficient consideration for the different subtypes
- Use of non-serotonergic drugs
- Inadequate dose of SSRI
- Inadequate time of administration during the acute and the maintenance phase
- Early discontinuation of treatment after response/remission
- Insufficient consideration for comorbidity
- Scarce consideration of a possible medical or neurological condition associated
- Scarce consideration for the efficacy/tolerability profile
- Lack of consideration for alternative strategies in case of scarce or no response

Conclusions

- Treatment effect on SSRI partial and dose and time dependent
- Long-term SSRI protects against relapse
- Possible benefit from SRI-ERP combined
- Developing role for antipsychotics
- High dose SSRI may be an effective alternative to AP
- New, more highly effective treatments targeting core symptoms desirable

Promising pharmacological treatments warranting further systematic study in resistant OCD

High-dose SSRI

Adding other antipsychotics, aripiprazole, amisulpride, ziprasidone

Opiate receptor agonists

Adding Glu/NMDA- agonists/antagonists (D-cycloserine, memantine, N-acetyl cysteine, riluzole, glycine)

Adding topiramate, pregabalin

Cognitive enhancers (d-amphetamine, methylphenidate, modafinil)

5-HT receptor antagonists (5-HT2c, 5-HT3)

Immunoglobulins and plasmapharesis

Deep brain stimulation (Now approved by FDA)

Neurosurgery (gamma knife surgery)

FUTURE HORIZONS

IMMUNE SYSTEM

- *CHILDHOOD*

- *ADULTHOOD*

GLUTAMATE SYSTEM

IMMUNE SYSTEM

- *CHILDHOOD*

PANDAS (driven by group A β-hemolitic streptococcus)

D8/17 ????

ANTIBIOTICS?

- *ADULTHOOD*

- Decreased T-cells, CD4+, NK, IL-1beta levels
- Increased CD8+ levels

GLUTAMATE SYSTEM

- Glutamate is one of the main neurotransmitters of the cortical-striatal-thalamo- cortical circuitry

-Animal models

-MRI studies show higher amount of glutamate in left caudate and ACC

-Higher CSF glutamate levels

-Genetic association studies (SLC1A1 encoding one glutamate carrier , GRIN2B encoding NMDA.2B subunit)

-PHARMACOLOGICAL DATA

GLUTAMATE SYSTEM

PHARMACOLOGICAL DATA

-D-cycloserine (partial NMDA agonist)

-Riluzole (antagonist inhibiting the Na and Ca channel and reuptake enhancer)

-Memantine (non-competitive NMDA receptor antagonist)

-N-acetylcysteine (Substrate ofr teh glutamate antiporter)

-Topiramate

-Lamotrigine

-Amantadine (NMDA antagonist)

GLUTAMATE SYSTEM

D-cycloserine (partial NMDA receptor agonist): effective in combination with exposure therapy

<u>Bias</u>
a. What is its optimal dose?
b. How long does its therapeutic effect last?

GLUTAMATE SYSTEM

- Riluzole (antagonist inhibiting the voltage-dependent Na and the P/Q type Ca channels and reuptake enhancer)

Bias

Only case reports in children and adolescents

-Memantine (non-competitive NMDA receptor antagonist)

Effective in resistant OCD (15-20 mg/die)

Bias

Open-label trials

GLUTAMATE SYSTEM

- *N-acetylcysteine (converted to cystine that is a substrate of the glutamate/cystine antiporter of glial cells laeding to incresaed extaracellular glutamate concentrations and decreased release)*

Bias

a. One case report only augmenting fluoxetine

b. One male patient only

GLUTAMATE SYSTEM

- *Topiramate (inhibitor of glutamate neurotransmission) tested in open and controlle trials*

Bias

Small samples

- *Lamotrigine (effective as augmenting strategy)*

Bias

Dermathological reactions

- *Amantadine (NMDA antagonist)*

Bias

Psychosis_inducer in elderly or medically-ill patients

IMMUNE and GLUTAMATE SYSTEMS

- Glutamate is a regulator of T-cell functions

Possible effectiveness of Cox-2 inhibitors (transforming arachidonic acid in prostaglandin H2 that is converted in different inflammatory mediators) in OCD.

Cox-2 inhibitors, through glutamate, decrease the production of pro-inflammatory cytokines and neuronal death induced by kainic acid

Celecoxib augments fluoxetine effectiveness and decrease the therapeutic latency

IMMUNE, SEROTONIN and GLUTAMATE SYSTEMS

•The immune system may activate indoleamine-deydrogenase (IDO) enzyme that shifts tryptophan from the synthesis of 5-HT towards that of kynurenines and quinolinic acid. Kynurenines themselves may induce excitoxic effects at the level of NMDA-type receptors