Clinical researches on Depression in Japan. Naturalistic studies, Drug trials, Treatment studies

- How do we accept the research evidences and change our practice? -

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Declaration of interest

- The speaker's hospital has/had research contracts with Fujimoto, GSK, Janssen, Lily, Mochida, Shinogi, Solvey, Suntory, Wyth.
  - We have randomized over 100 patients in three years.
  - Currently we are conducting placebo controlled trial for GAD with GSK.
- This is a Luncheon seminar sponsored by GSK.
- The sale of antidepressants is growing.

World total of 14 items		¥1,800 bill	Japan ¥ 60 bill
Paroxetine	£ 1877mil	¥ 359 bill	Japan ¥ 23 bill
Zoloft	$ 3118mil	¥ 332 bill	
Fluvoxamine	€ 80mil	¥ 10 bill	Japan ¥13.5 bill
Toledomin			Japan ¥ 6 bill

World 2002, Japan 2003 http://www.fukumi.co.jp/mm/add/1050_add.htm

Objectives of this presentation

- Didactic; Inform you about
  - Researches in Japan
    - Paroxetine RCT
    - Paroxetine study with QOL measure
    - Systematic review of antidepressants by Inada T.
    - Naturalistic cohort study by Group for Longitudinal Affective Disorders, Furukawa T.
  - Current challenges of treatment researches for depressive disorders
- Heuristic
  - Critical appraisal of the evidences
  - Clinical decision making

What usually thought of, If you hear “EBM”

- RCT
- Use realistic outcome measure
  - You have to measure the success of treatment not by symptom measure but patients’ perceived QOL.
- Systematic Review
- Longitudinal prospective cohort study
- Not in my backyard (in Japan?)

Evidence of Depression in Japan

1. Paroxetine vs. Imipramine RCT

   Aoba A et. al：Japanese Journal Clin. Psychopharm 7 (5) 831-835, 2004

2. Paroxetine Open study, outcome of QOL and the impact of comoribid anxiety disorders

   Aoba A et al：Jpn. J. Clin. Psychopharmacol, 7 (7) ,1169, 2004

3. Systematic review by Inada T.

   稲田俊也　ひと目でわかる向精神薬の薬効比較　じほう

4. Study by Group for Longitudinal Affective Disorders, Furukawa T.

Presentation 1
Paroxetine (PX) vs. Imipramine (IM) RCT

- Post-Marketing Surveillance for Paroxetine in patients with depression and depressive state
  -A double-blind comparative study with Imipramine-
- **Aoba A et. al：Japanese Journal Clin. Psychopharm 7 (5) 831-835, 2004**

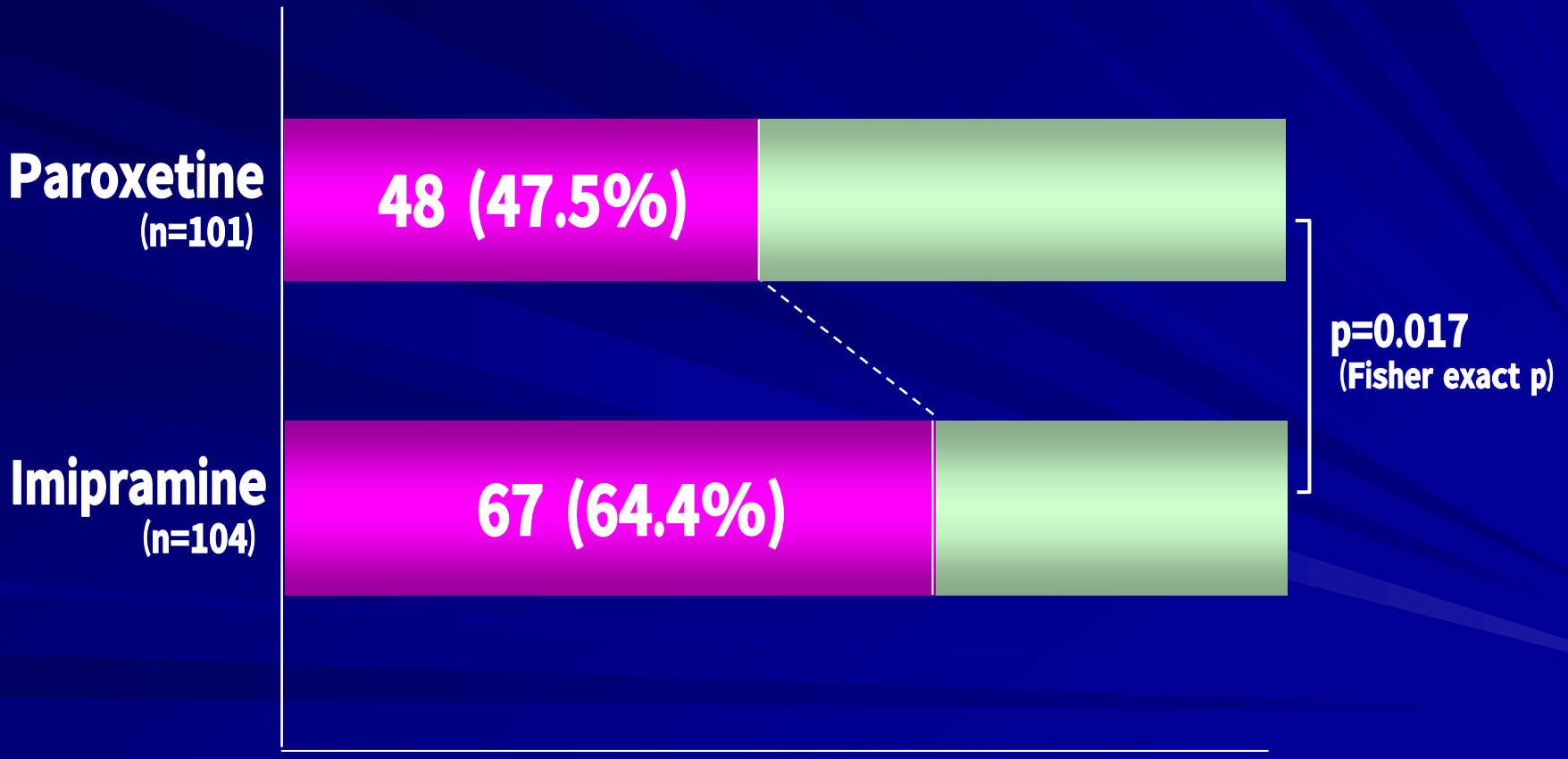
About this Research

- Objective
  - Does Paroxetine has lower anti-cholinergic side effects in comparison with Imipramine?
  - Comparison of Efficacy
- Subjects
  - Depressive disorders
  - Age 18 to 64
  - Patients who visited spontaneously
- Design
  - 40 centers collaborative, RCT, DB, 6 week
  - Flexible dose, Paroxetine 20 to 40 mg, Imipramine 50 to 150 mg.
- Endpoint
  - Incidence of anti-cholinergic side effects
  - HAM-D 17

Aoba A et. al : Japanese Journal Clin. Psychopharm 7 (5) 831-835, 2004

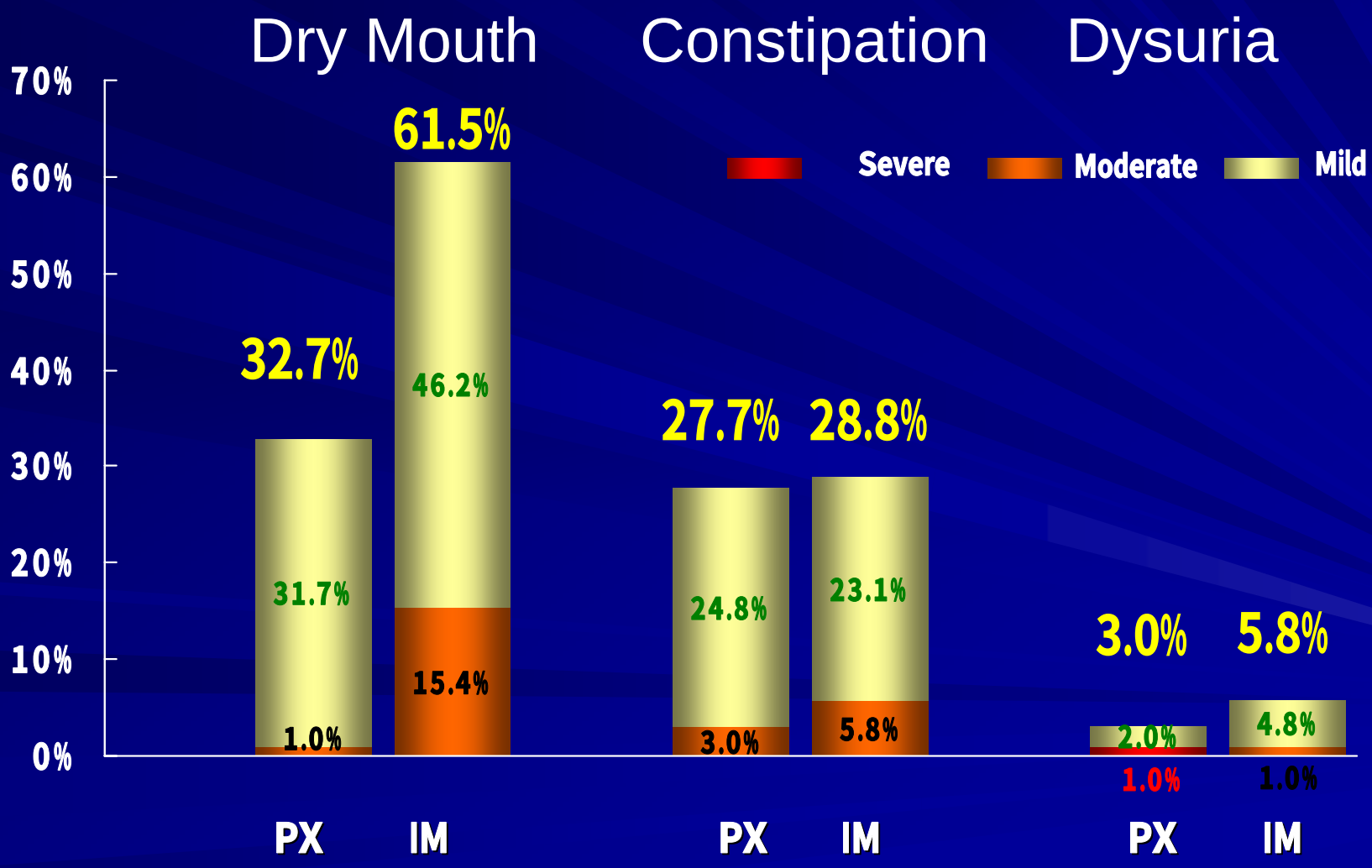
Anti-cholinergic side effect : Incidence

Dry mouth · Constipation · Dysuria



Aoba A et. al : Japanese Journal Clin. Psychopharm 7 (5) 831-835, 2004

Anti-cholinergic side effect : Severity

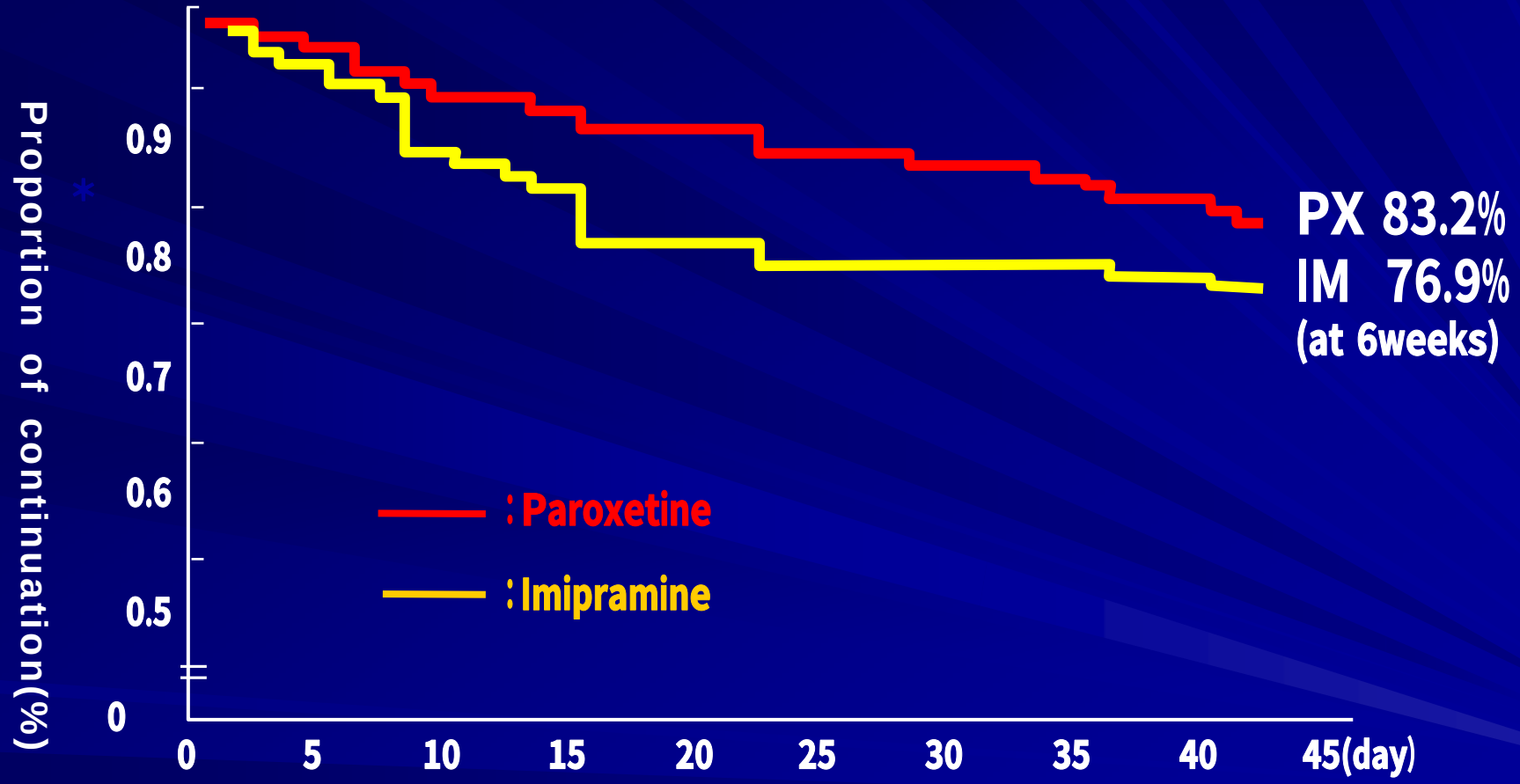


Overall side effects

- The incidence of total side effects
  - PX 74.3% IM 75.0%
  - Major side effects (incidence over 5%)
    - Common: Drowsiness, Nausea, Headache, Dizziness
    - PX: Sexual disturbance
    - IM: Cardiovascular
- Drop out due to side effects
  - PX 11.9% IM 15.4%

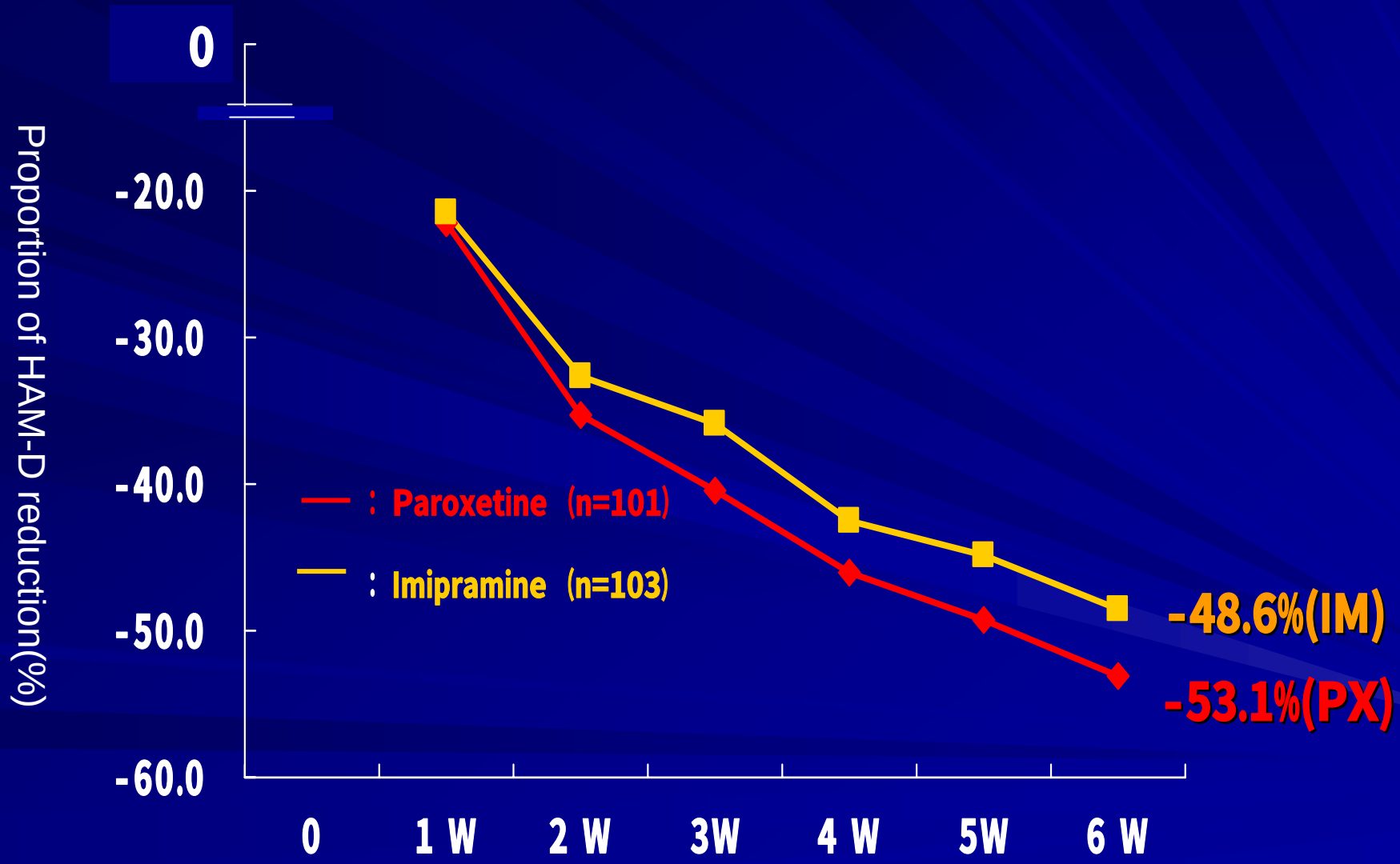
Aoba A et. al：Japanese Journal Clin. Psychopharm 7 (5) 831-835, 2004

The rate of Administration Continuation



Aoba A et. al：Japanese Journal Clin. Psychopharm 7 (5) 831-835, 2004

HAM-D Reduction Rate (Mean)



Exercise

- How do you think about this research?

Critical Appraisal

- Why did they start?
  - Worth reading on? Objective
- What did they do?
  - Any bias? Validity,
    - Randomization, Blind rating
- What did they find?
  - Results?
    - Post hoc sub group analysis is misleading
- What does it mean?
  - Is your question answered? Relevance

Appraisal

- What they find?
  - Anti-cholinergic side effects
    - PX < IM
    - Other side effects?
  - At 6 week HAM-D was

	PX	IM
Mean	7.7	9.4
Median	7	8

    - Drug response
      - Response :50% Reduction of HAM-D
      - Remission: HAM-D <= 7

Appraisal cont.

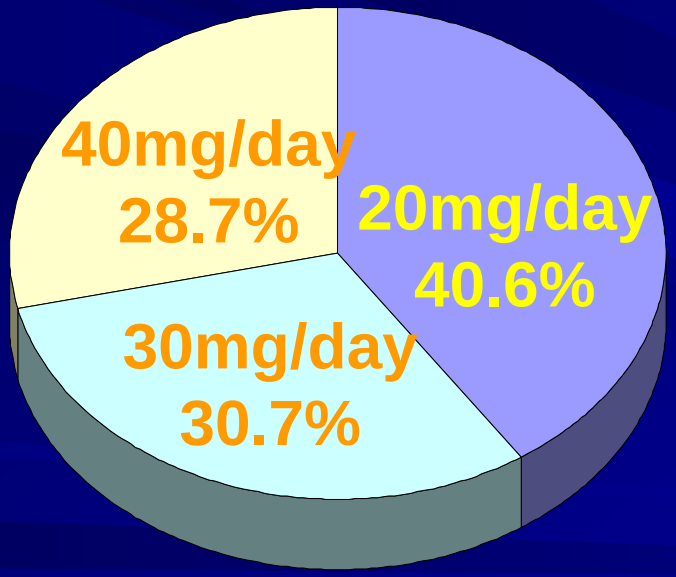
- What does it mean?
  - At 6 week, half of the subjects are not fully recovered in both groups (HAM-D >=7)
  - Was dose titration appropriate for both groups?
  - Do not remit does not mean treatment refractory. It may mean inadequate dosing of the drug.

Aoba A et. al：Japanese Journal Clin. Psychopharm 7 (5) 831-835, 2004

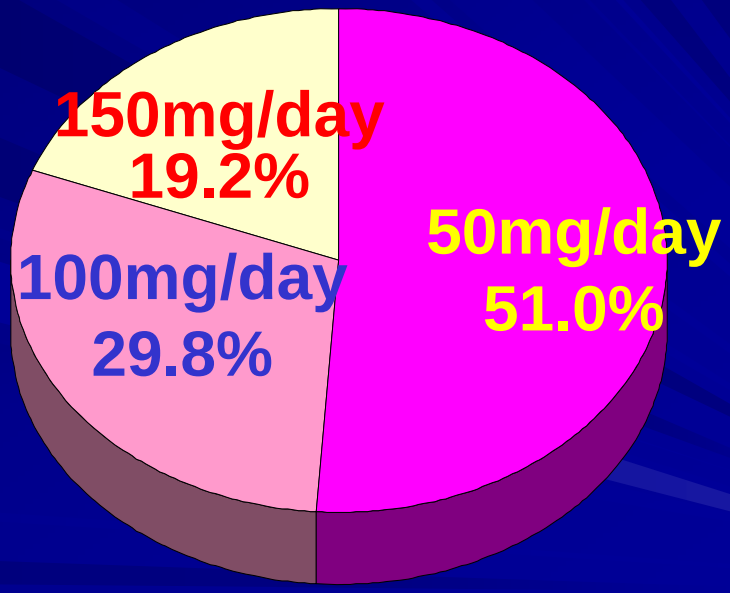
The Subjects & dose titration

- **Randomized Patients**
  - **Paroxetine 106,**

Imipramine 104



Paroxetine group :
28.8mg(±8.28) /day



Imipramine group :
84.1mg(±38.96) /day

Dose

- Dose titration was up to the physician
  - 59.4% of PX group increased dosage.
  - 49% of IM group increase dosage.
  - PXs typical therapeutic dosage is 20~40mg.
  - IMs typical therapeutic dosage is 150~300mg.
- You might observer better outcome, if dose were titrated to maximum level.

Appraisal cont

- Relevance
  - Subjects are excluded, IF
    - Suicidal
    - Did not sign to the informed consent
    - Meet other numerous exclusion criteria
  - Treatment
    - Weekly visits and HAM-D
    - No anxiolytics
    - Six weeks, and withdraw the drug
      - The subjects agreed with it at the beginning

Summary

- The profile of side effects is primary objective.
- Dose titration may not be appropriate.
  - This is observed in other settings too.
- The information of side effect profile is helpful to decide which drug to prescribe.

Dose titration among countries

- Dose titration is up to a physician's decision.
- In Japan, there are two SSRIs available.
- A survey of drug prescription pattern across countries
- Mean dosage /day in one prescription

	JP	Korea	Taiwan	China	HK	US	UK	Fr
paroxetine	23.9	22.8	25.8	25.8	22.8	22.6	23.3	23.4
fluvoxamine	70	73.5	132.8	73.5	118.1	144.1	177.2	120.7

Presentation 2
Evaluation of Health Related QOL in Japanese Patients with Depression or Depressive Episodes Treated with Paroxetine

- An Open-label Multi-Center Clinical Study of Paroxetine

  Aoba A et. al；Japanese Journal Clin. Psychopharm 7 1169-1192, 2004

About the research

- Objective
  - Evaluate health related QOL with SF-36 in patients with depression in Japanese population
  - Explore the benefit of Paroxetine treatment on QOL
- Design
  - 22 centers, open label
- Subjects
  - 178 patients
  - Inclusion criteria
    - HAM-D >= 16
    - 18 to 64 yrs old
    - Singed to the informed consent
  - Exclusion criteria
    - Suicidal, Bipolar disorder, Substance use disorder
    - Other physical / mental conditions which are contra-indication for study drug.

SF-36 Health status scales

Physical Health	**Physical Functioning**	**Perform all types of physical activities or Limited a lot due to health**
	Physical Role Functioning	**No problem or Problem with work or other daily activities as a result of physical health**
	Bodily Pain	**No pain or limitations due to pain Very severe and extremely limiting pain**
	General Health	**Evaluates personal health as excellent or as poor**
Mental Health	**Vitality energy vs. fatigue**	**Feel full of pep and energy all of the time Feels tired and worn out all of the time**
	Social Functioning	**Performs normal social activities without interference due to physical or emotional problems**
	Role-Emotional	**No problem or Problem with work or other daily activities as a result of emotional problems**
	Mental Health	**Feels peaceful, happy, and calm Feeling of nervousness and depression all of the time**

Method

Dosage and Administration : Initial dosage 10 or 20mg/day, flexible-dose

■ Observation Schedule

M.I.N.I.	★												
SF-36	★			★				★				★	
HAM-D	★			★				★				★	

M.I.N.I. : The Mini International Neuropsychiatric Interview SF-36 : MOS 36-Item Short-Form Health Survey
HAM-D : Hamilton's Rating Scale for Depressin

Aoba A et al: Jpn. J. Clin. Psychopharmacol, 7 (7) ,1169, 2004

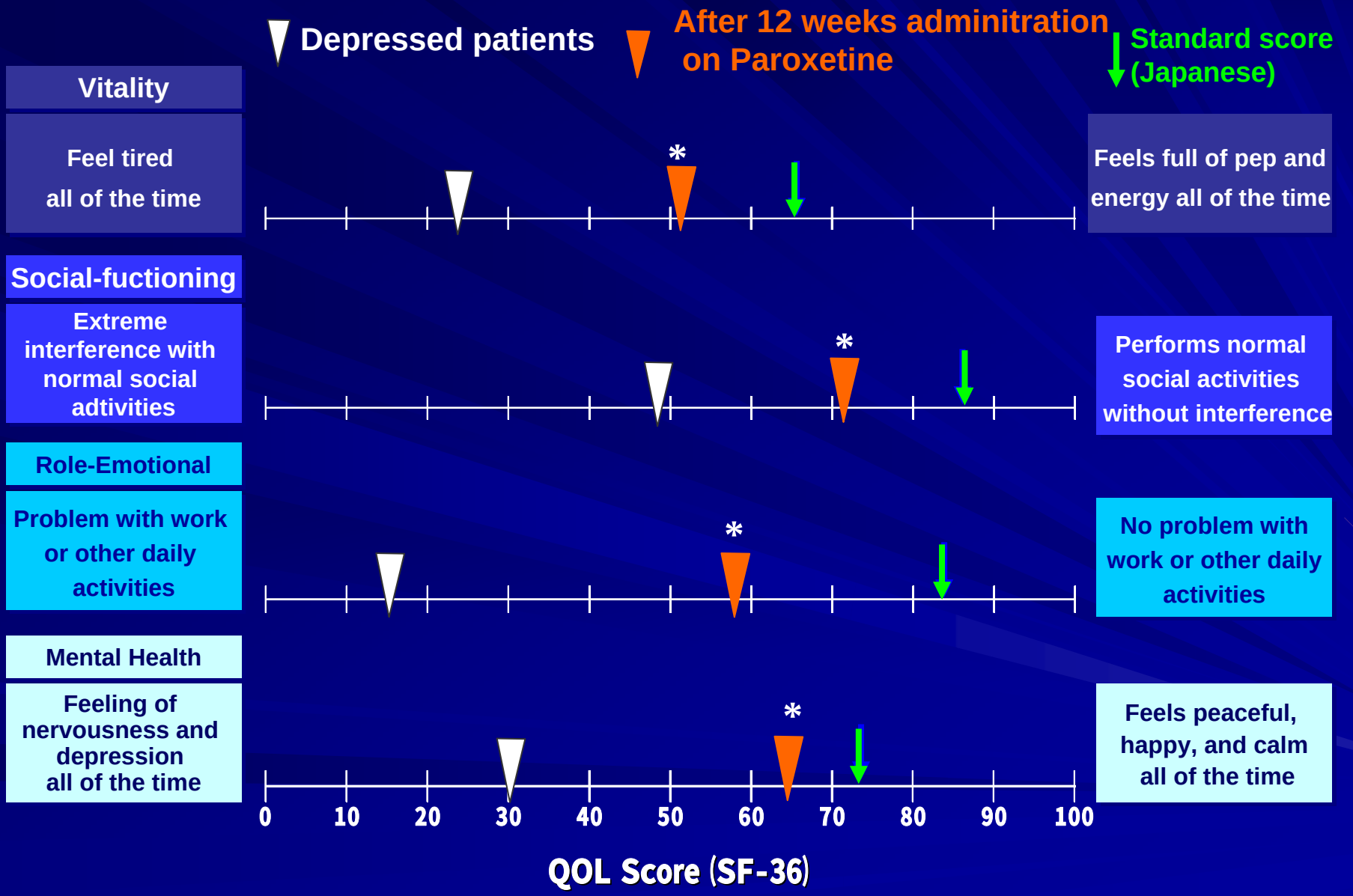
Result

- Diagnosis
  - MDD single episode 60.1%
  - MDD recurrent 27.5%
  - Dysthymic disorder 9.0%
  - DD NOS 3.4%
- HAM-D score
  - Mean 22.0

Comorbid Anxiety Disorders

Any anxiety disorder	55 (31%)
Panic	20 (11%)
SAD	26 (15%)
OCD	17 (10%)
GAD	12 (7%)
PTSD	10 (6%)

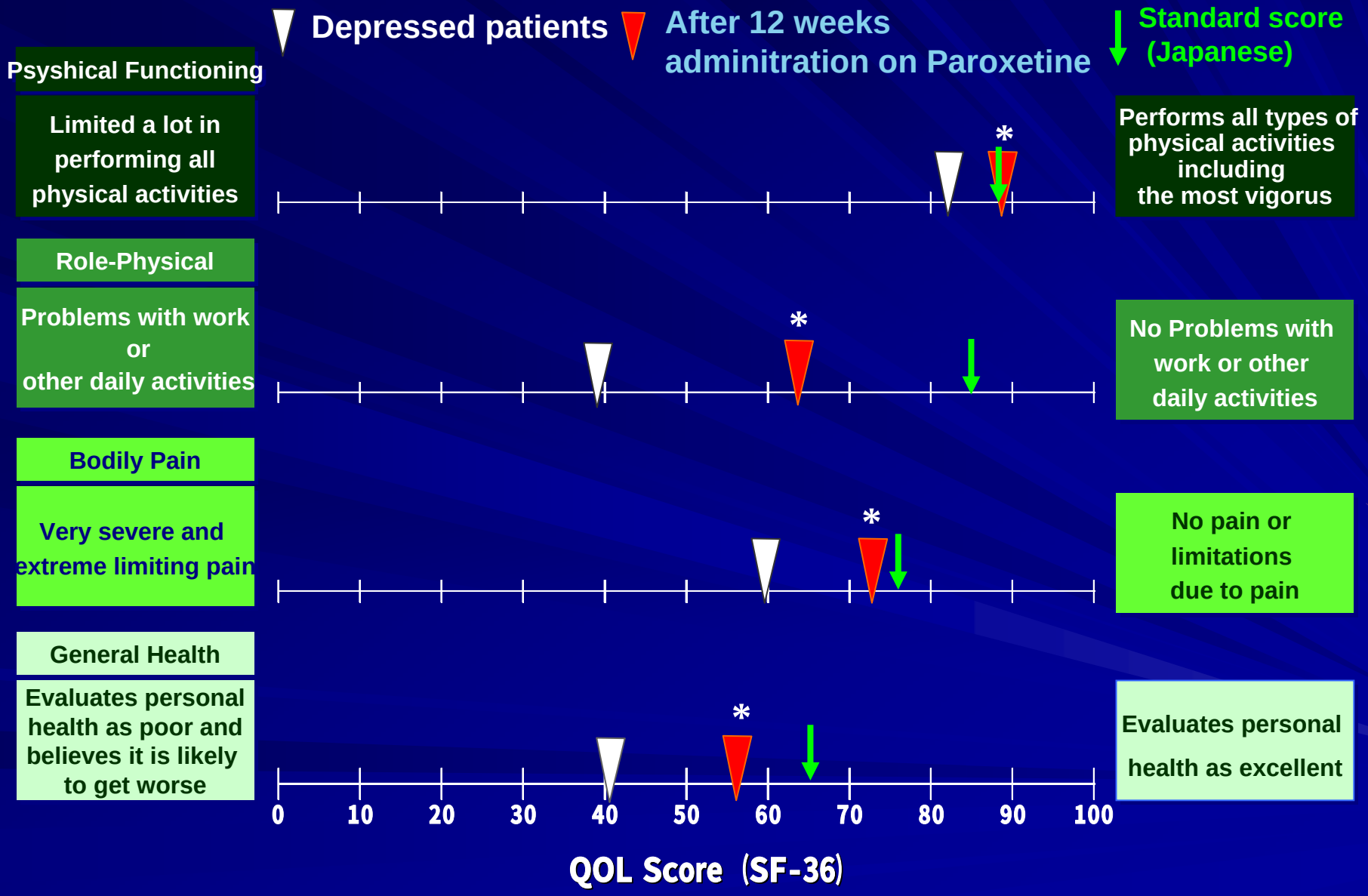
The outcome of SF-36 (Mental Health)



*：p＜0.0001（vs. before treatment）　(n = 178)

Aoba A et al：Jpn. J. Clin. Psychopharmacol, 7 (7) ,1169, 2004

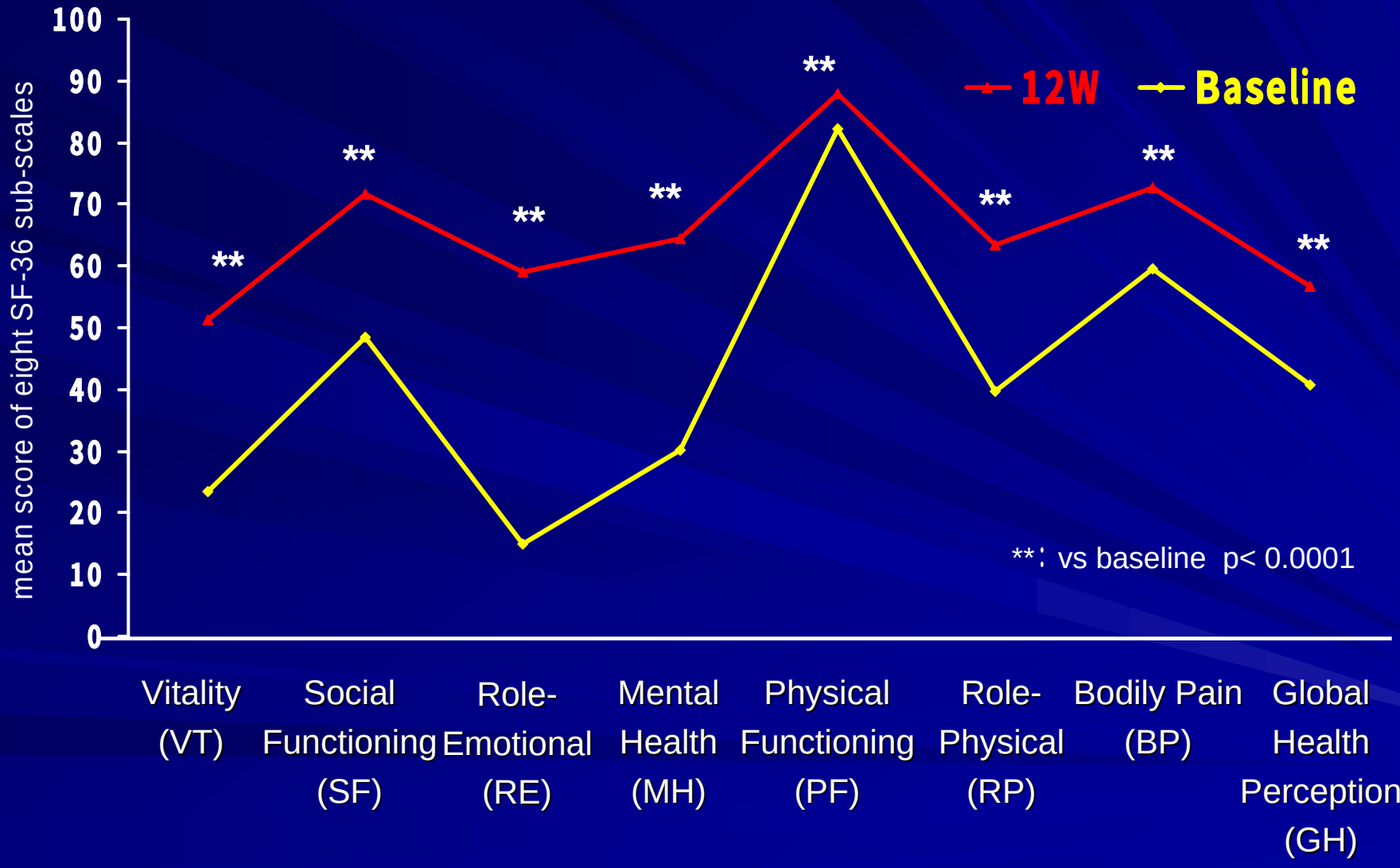
The outcome of SF-36 (Physical Health)



*：p＜0.0001 (vs. before treatment)　(n = 178)

Aoba A et al：Jpn. J. Clin. Psychopharmacol, 7 (7) ,1169, 2004

Mean score of eight SF-36 sub-scales by Paroxetine at baseline & 12weeks after

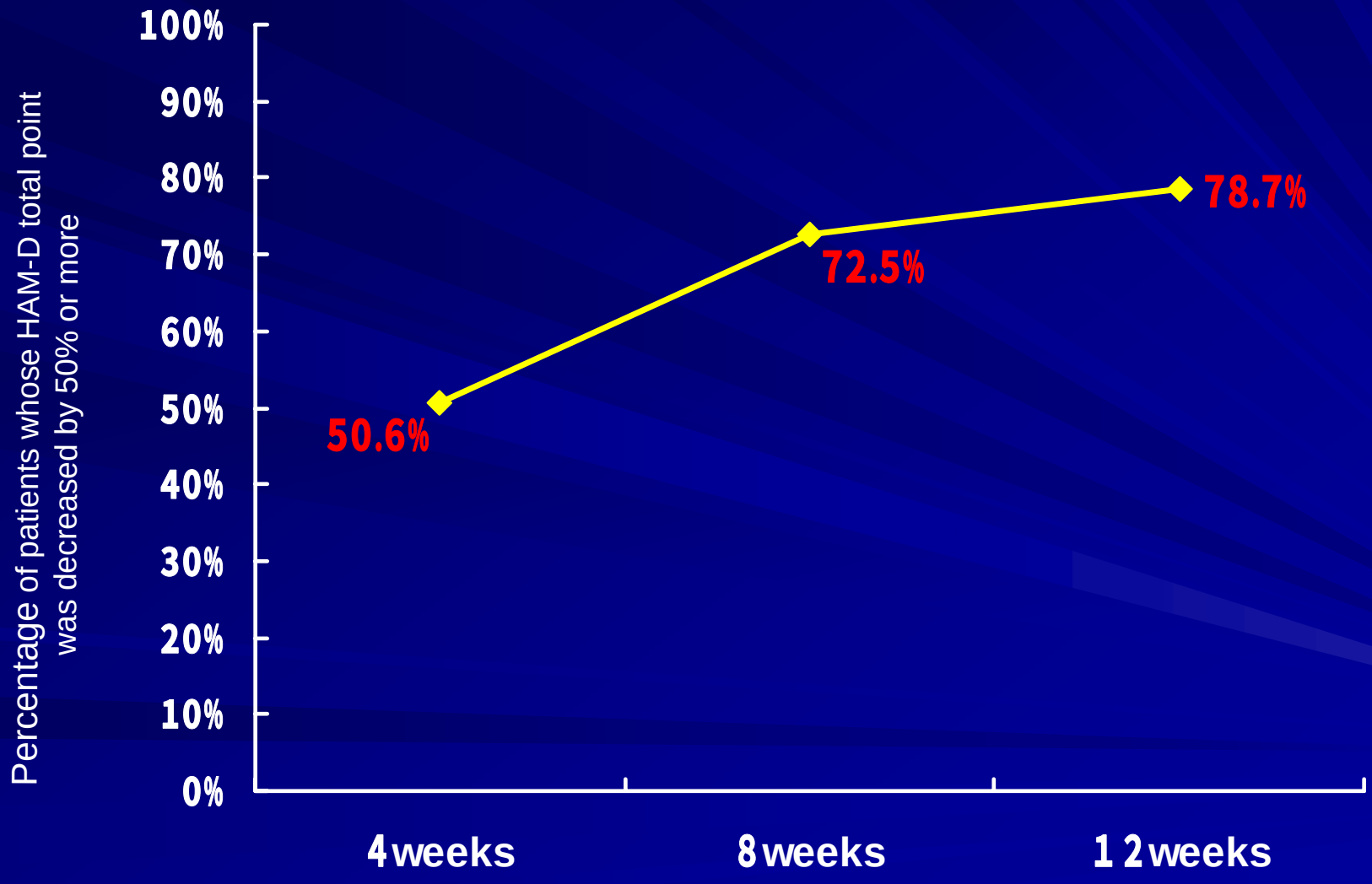


N=178

Aoba A et al: Jpn. J. Clin. Psychopharmacol, 7 (7) ,1169, 2004

Time-course change of percentage of patients who respond to paroxetine

(decrease rate of more than 50% in HAM-D total score)



Aoba A et al: Jpn. J. Clin. Psychopharmacol, 7 (7) ,1169, 2004

Percentage of patients who remit (HAM-D is 7 or less)

Aoba A et al: Jpn. J. Clin. Psychopharmacol, 7 (7) ,1169, 2004

Critical Appraisal

- This research gives us the estimate of utility.
- Utility is;
  - A continuum of
    0 dead / totally disabled - 100 perfect health
- Important to do decision analysis

Presentation 3 Systematic Review

編集･解説

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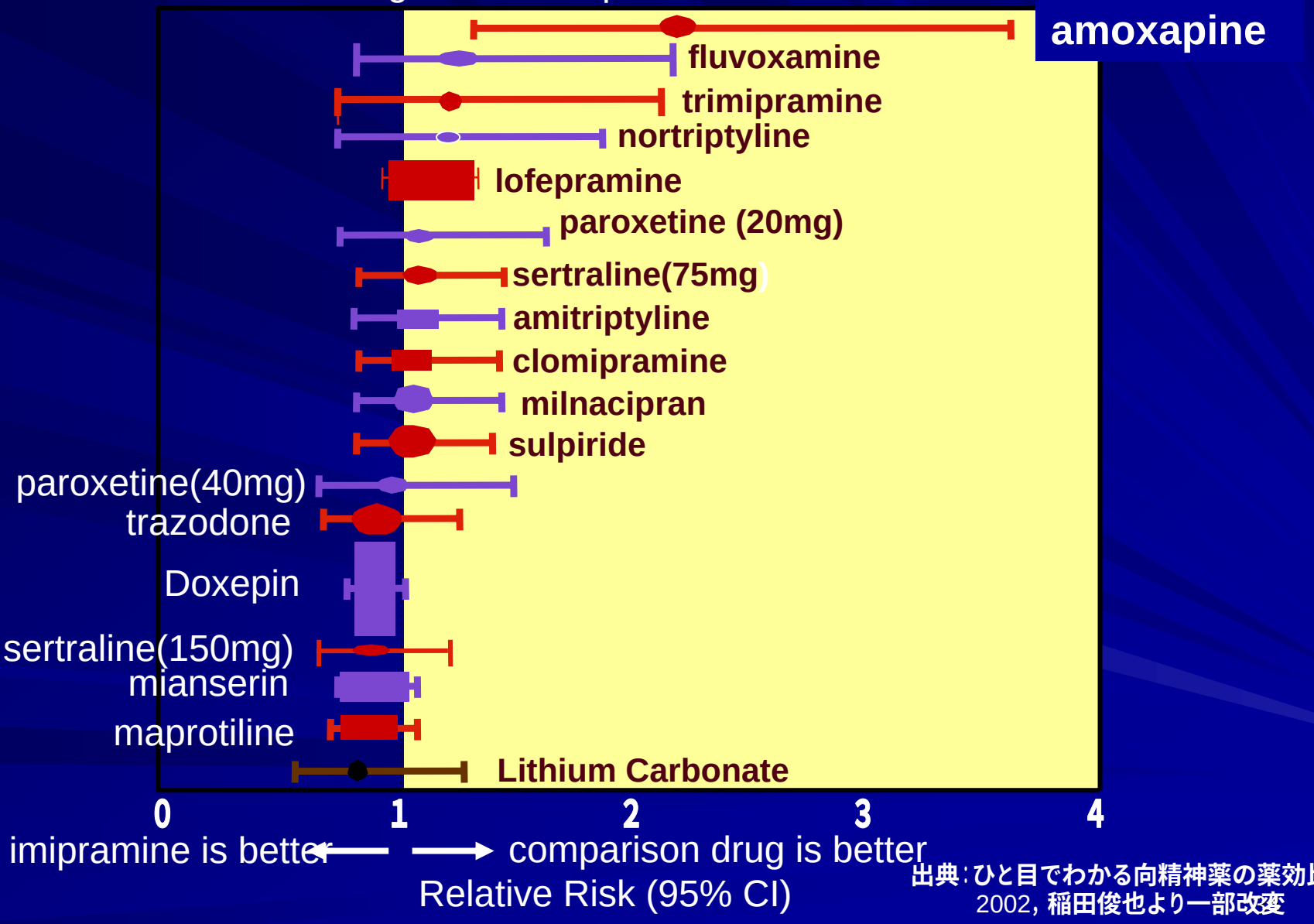
出版社:じほう

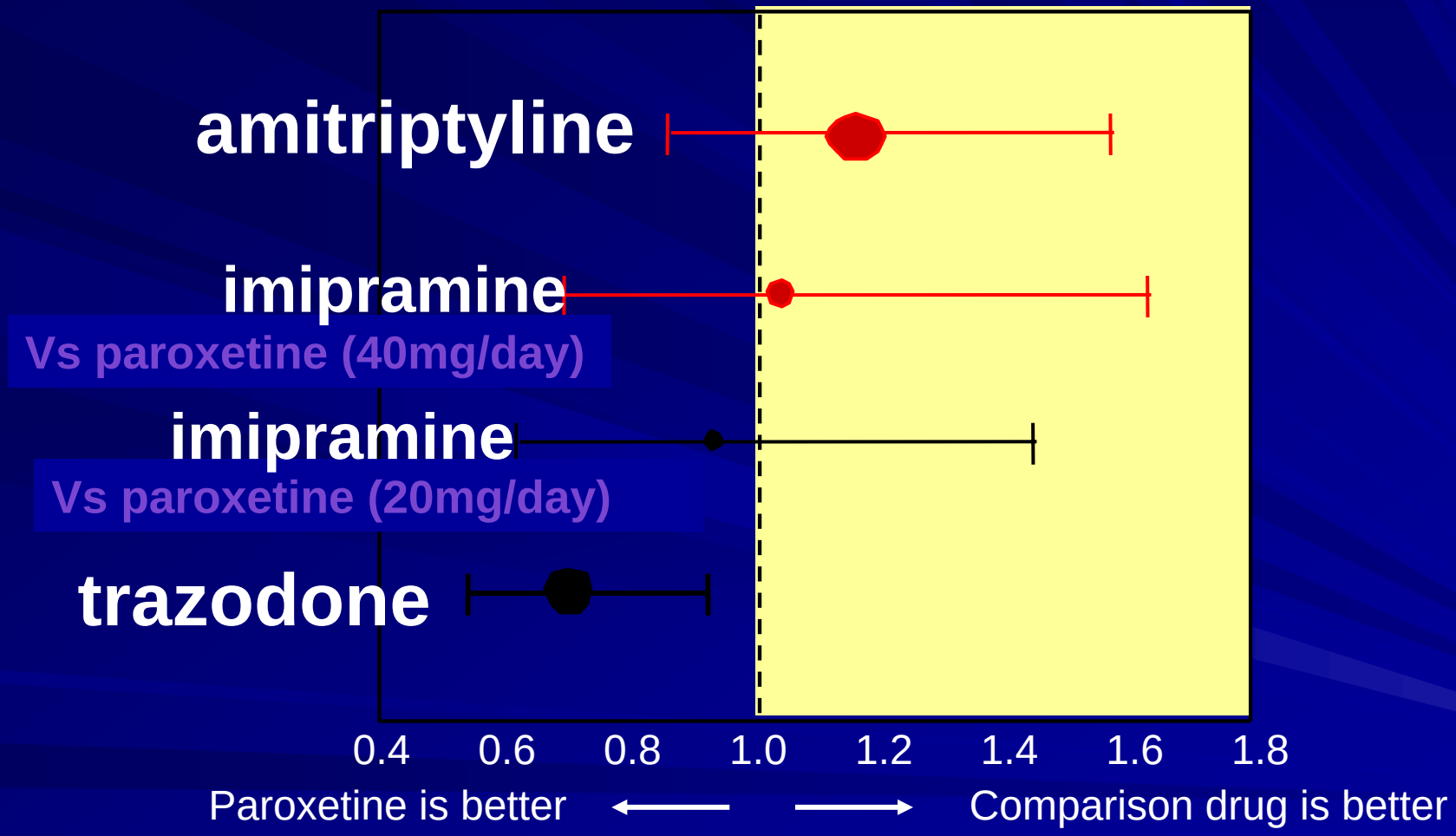
Comparison with Imipramine

Target:MDD, Depressive state

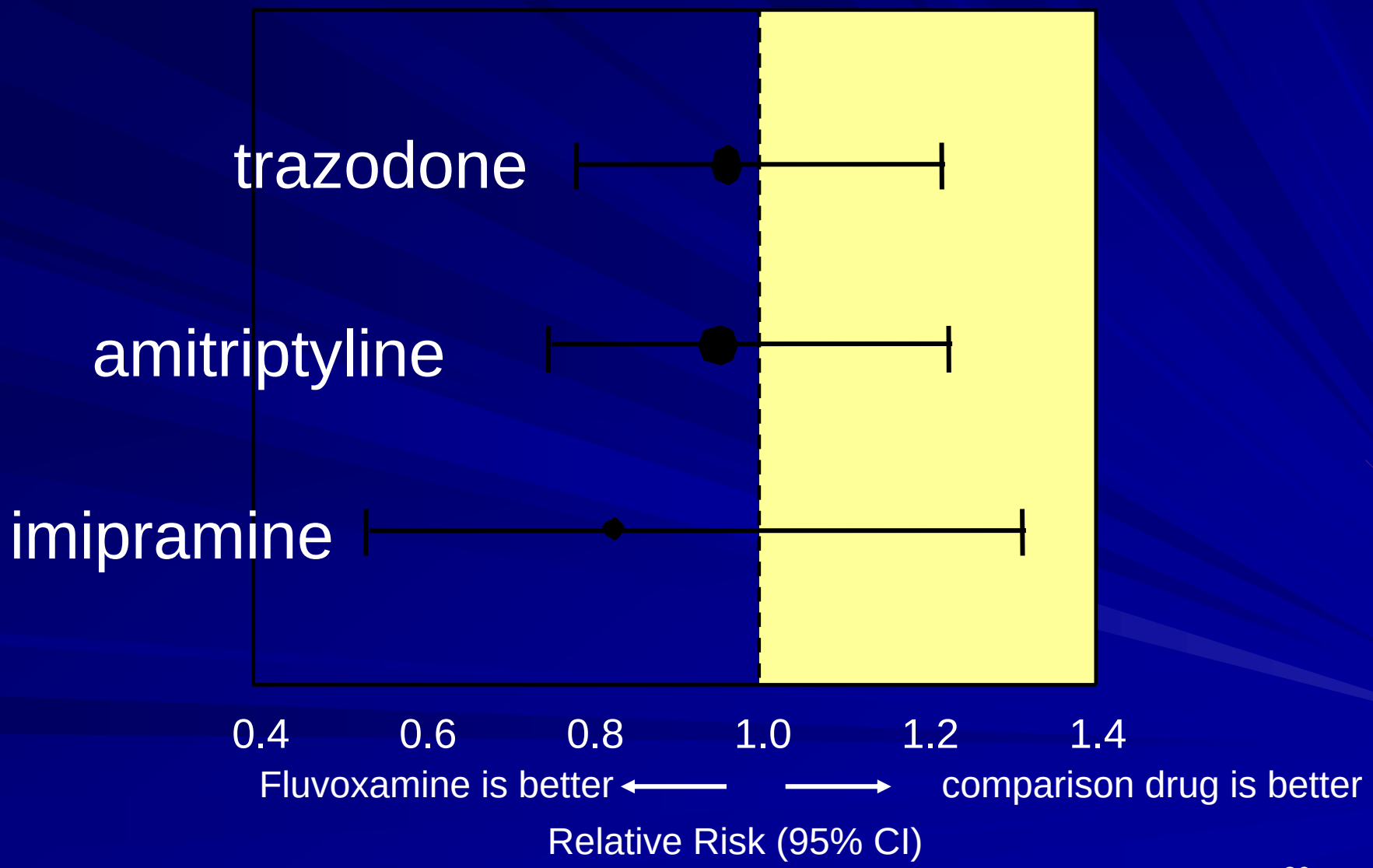


出典：ひと目でわかる向精神薬の薬効比較
2002，稲田俊也より一部改変

Comparison with Paroxetine



Comparison with Fluvoxamine



In Summary

- Statistically different
  - Amoxapine > Imipramine
  - Paroxetine > Trazodone
- Overall
  - “Do-do bird verdict”
- Get more skeptical
  - Comparison with placebo
  - Comparison with psychotherapies

Presentation 4

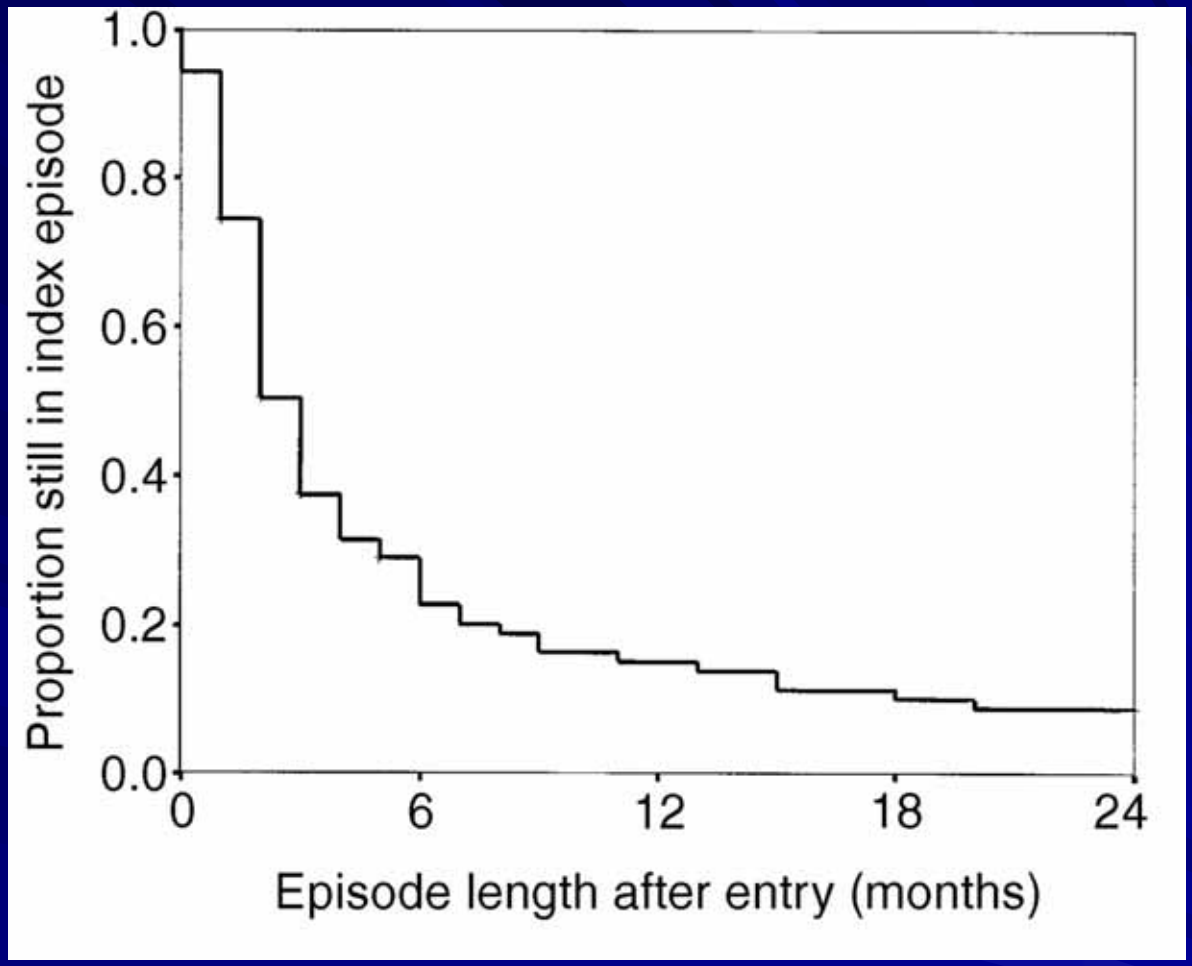
Natural course of depressive episode

GLADS research lead by Furukawa TA

- Time to recovery of an inception cohort with hitherto untreated unipolar major depressive episodes
  - Br J Psychiatry. 2000
- Treatment received by depressed patients in Japan and its determinants: naturalistic observation from a multi-center collaborative follow-up study
  - Journal of Affective Disorders 2000

Time to recovery without antidepressants

- Median time to recovery of the index episode after treatment commencement
  - 3 months (95% CI 2.5-3.6)
- Median time to recovery from the onset of the index episode
  - 7.0 months (95% CI 5.2-8.8).



Cumulative probability of remaining in the index episode after treatment commencement for the 90 probands with DSM-IV major depressive disorder not superimposed on dysthymia. Patients who recovered within a few days after treatment commencement were regarded as attaining recovery at 0 month.

Recent world literatures

- Several years ago
  - Safe, Efficacious Drug were invented
  - Depression is a big pervasive problem and under-treated
  - Treatments works
  - Find them and get them straight fully
- Now
  - Time to contemplate

Review of literatures

- Do antidepressants really benefit?
  - Placebo response in depression: bane of research, boon to therapy
    - Andrew G, British Journal of Psychiatry (2001)
  - 60% of drug effect can be explained by placebo effect
  - Three reason of placebo effects
    - Encouragement
    - Depression is self remitting condition
    - Depressive people seek treatment when they feel hopeful, they do not seek help when they are at the bottom, totally hopeless.

Current State of “Evidence”

- Awareness of the limitation of published RCTs.
  - Tells only Efficacy, not Effectiveness
  - Publication bias
- Challenge for the researchers
  - Translational research, Population based studies, Claim based studies, Realistic RCTs
  - Case studies informed with evidence

“Do-Do bird verdict”

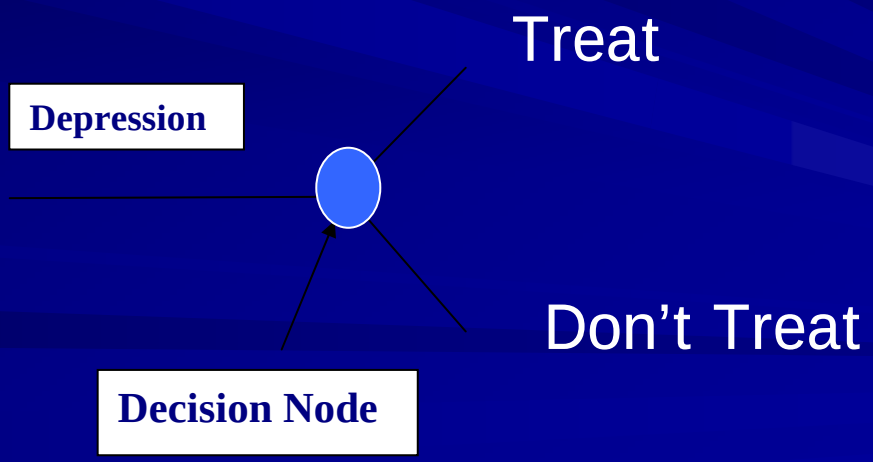
- Almost all antidepressants have same efficacy.
- Does not mean an individual patient responds equally to any antidepressants.
  - Problem is there is no way to predict, unless you know the previous.
  - Drug treatment is a N=1 trial.
  - You can predict the side effect matching.

Using Evidence

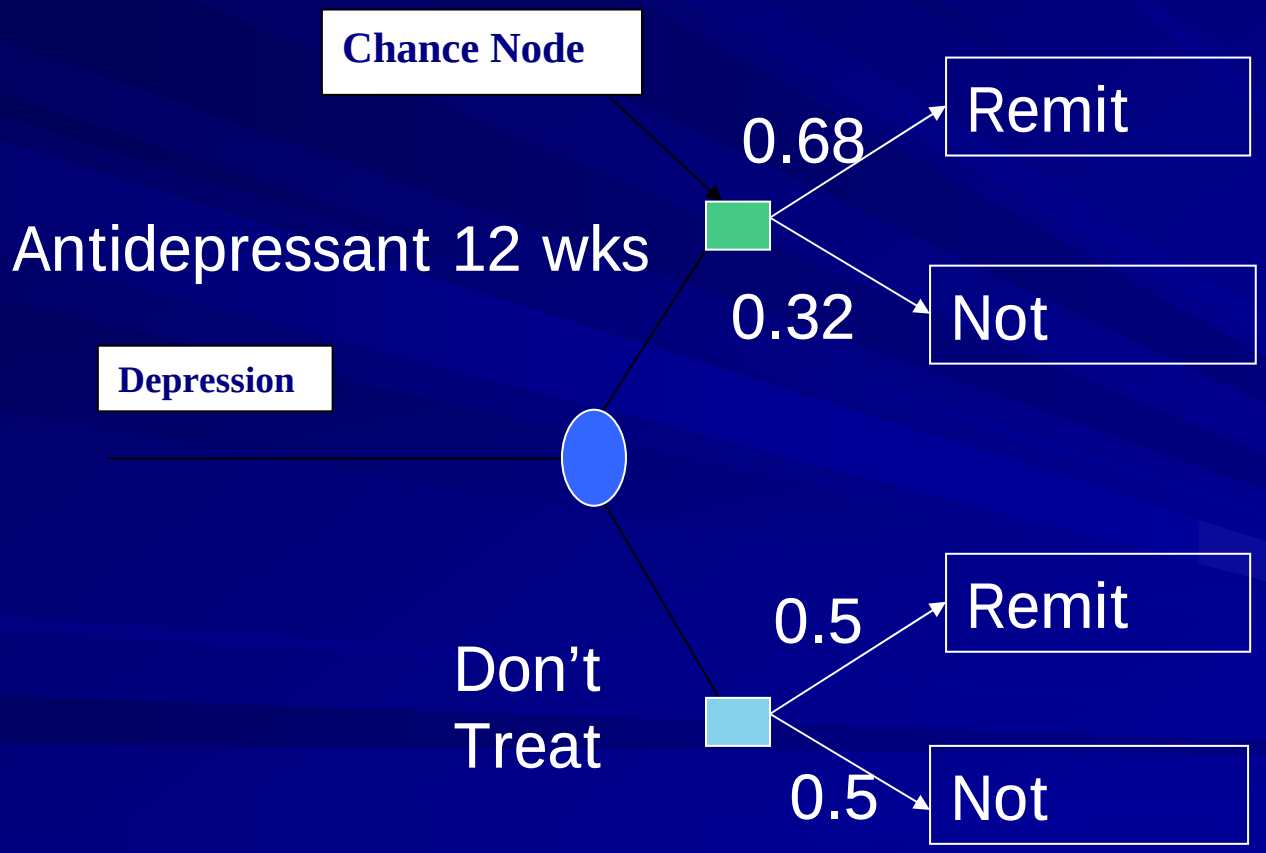
- As a clinician
  - Clinical decision making
    Decision analysis can help
- What is Decision Analysis?

How does one start?

- List all the options and display probability and utility.
  - Utility is on continuum 0 worst 100 complete health.
- Tree diagram or Table



Decision data



Add reality to probability scores

- Benefit of the treatment
  - Utility
- Cost of treatment
  - Side effects
  - Price
- Cost of physician
  - Physician must explain you are depressed
- Multiply the probabilities by the utility

Decisional balancing

- At 12 weeks Event x probability x utility
  - Utility is 0 to 100, 78 was chosen as standard of normal population in Japan.

	PX	Observe
Benefit	Recover 0.68 x 78	Recover 0.5 x 78
Harm	Any side effects 0.64 x -20 (?)	Zero
Total	40.2	39

Applying Evidence to Decision making

- Case 1
  - Age 38 Male. Five previous depressive episodes from age 34
  - Cc Depressive mood, Suicidal ideation, Lethargy, Sleep disturbances, Referred from a clinic to have CBT.
  - HAM-D17 = 23
  - MDD recurrent
- Case 2
  - Age 25 Female.
  - Cc Depressive mood , Guilt, Sleep disturbances, Physical complaints, Sex dependence
  - HAM-D17 =13
  - Dysthymic disorder

Case 1

- Life chart

Age	34	36	36	37	38	38	39
Event	First episode Visit clinic, recovered by 6 months	Married	2nd episode	3rd episode, suicidal attempt	4th episode	5th episode	Referred

- Summary of previous treatment trial
  - Max dose: sulpiride 300, Clomipramine 75, Fluvoxamine 150, Amitriptyline 100, Paroxetine 20, Milnacipran 100, Mianserin 150, Maprotiline 50 and anxiolytics
  - Continued medication for 5 years

Case 1 cont.

- Very sensitive to dysuria.
- TCA has never tried to the therapeutic dose
- Start Nortriptiline 50mg to 150 mg
  - 8 weeks after HAM-D 16, not enough response
- Add Lithium carbonate 400mg
  - 12 weeks after HAM-D 3
  - Maintained recovery for 3 years
- Recently switched to Paroxetine 40mg

Case 2

- Start Paroxetine 20mg
- 8 wks later
  - HAM-D 11, Sexual drive suppressed (Subjective measure 100 → 20)
- 12 wks later
  - HAM-D 10, increase dosage to 40mg
- 18 wks later
  - HAM-D 3, Abstinence for a month

An attitude

- You must tolerate uncertainty
- Everything is proportional

- Three principles

  (1) Compare: Within patient, Within episode

  (2) Repeat: Assessment

  (3) Try out

- Tools
  - Life chart method
  - Decisional balancing

In conclusion

- Multiple Choice Questions

Q1. Relating to the quality of evidence available from treatment

a RCTs are designed to minimize the effects of bias on outcomes

b The results of RCTs can be accepted at face value

c The nature of the outcome measures used in psychiatry means that the results are usually robust

d Unreplicated small studies should not be trusted

e RCTs usually involve typical patients

answers

1. a T, b F, c F, d T, e F

Anderson IM; Advances in Psychiatric Treatment (2003), 9.11-20

Q2 Patients are likely to benefit from being treated with an antidepressant rather than placebo in:

a Severe major depression

b Minor depression

c Dysthymia

d Mild major depression

e Chronic major depression

Answers

2. a T, b F, c T, d F, e T

Anderson IM; Advances in Psychiatric Treatment (2003), 9.11-20

Q3. Reasonable strategies in patients not responding to 6 weeks' treatment with an antidepressant include:

a Continuing the same treatment

b Increasing the dose

c Switching antidepressant

d Augmenting the antidepressant with another drug

e Combining antidepressants.

answers

3. a T, b T, c T, d T, e T

Anderson IM; Advances in Psychiatric Treatment (2003), 9.11-20

Q4 In studies of antidepressant augmentation/combination for treatment-resistant depression:

a Lithium augmentation has the strongest evidence base

b Pindolol augmentation is clearly effective

c Combination of a monoamine reuptake inhibitor with mianserin/mirtazapine may be useful

d Tri-iodothyronine augmentation is clearly ineffective

e Studies of augmentation with tryptophan are uniformly negative.

answers

4. a T, b F, c T, d F, e F

Anderson IM; Advances in Psychiatric Treatment (2003), 9.11-20

Q5 In continuation/maintenance treatment with antidepressants:

a All patients should continue for 6 months on an antidepressant after remission following acute treatment

b Patients with more than two episodes of major depression should routinely have maintenance antidepressants for at least 5 years

c Continuing antidepressant treatment appears to reduce the risk of relapse and recurrence by a similar proportion, whatever the underlying risk

d The underlying risk of relapse should not be a major factor in the decision to continue antidepressant treatment

e Advice about continuing antidepressants should be individually tailored to each patient's circumstances as far as possible.

answers

5. a F, b F, c T, d F, e T

Anderson IM; Advances in Psychiatric Treatment (2003), 9.11-20

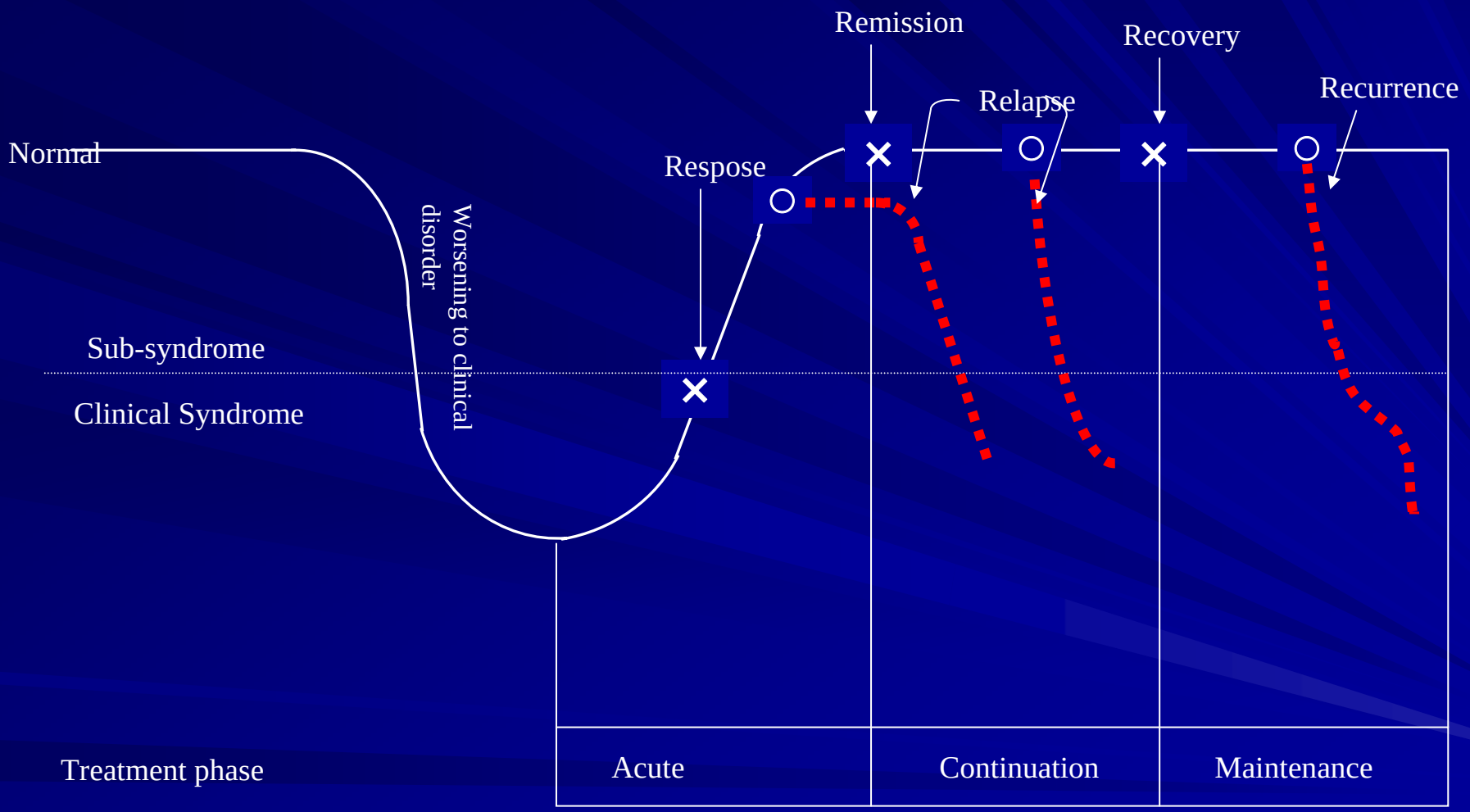
Final note

- Thanks Aoki san
- Thanks Prof. Nakane
- Q & A

E-mail: hharai@cup.com

www.hosp.go.jp/~kikutihp/
homepage1.nifty.com/hharai/

Phase and outcome of depressive episode



Kupfer,D.J.: J.Clin. Psychiatry, 52(5,suppl.):18,1991