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

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

HARAI Hiroaki
Kikuchi National Hospital, Division of Clinical Research
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

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

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

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-

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
Dry Mouth  Constipation  Dysuria
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%
Proportion of HAM-D reduction (%)
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

<table>
<thead>
<tr>
<th></th>
<th>PX</th>
<th>IM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>7.7</td>
<td>9.4</td>
</tr>
<tr>
<td>Median</td>
<td>7</td>
<td>8</td>
</tr>
</tbody>
</table>

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.
The Subjects & dose titration

- **Paroxetine group**: 28.8mg (28.8mg) /day
  - 20mg/day: 40.6%
  - 30mg/day: 30.7%
  - 40mg/day: 28.7%

- **Imipramine group**: 84.1mg (84.1mg) /day
  - 50mg/day: 51.0%
  - 100mg/day: 29.8%
  - 150mg/day: 19.2%
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

<table>
<thead>
<tr>
<th></th>
<th>JP</th>
<th>Korea</th>
<th>Taiwan</th>
<th>China</th>
<th>HK</th>
<th>US</th>
<th>UK</th>
<th>Fr</th>
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</thead>
<tbody>
<tr>
<td>paroxetine</td>
<td>23.9</td>
<td>22.8</td>
<td>25.8</td>
<td>25.8</td>
<td>22.8</td>
<td>22.6</td>
<td>23.3</td>
<td>23.4</td>
</tr>
<tr>
<td>fluvoxamine</td>
<td>70</td>
<td>73.5</td>
<td>132.8</td>
<td>73.5</td>
<td>118.1</td>
<td>144.1</td>
<td>177.2</td>
<td>120.7</td>
</tr>
</tbody>
</table>
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

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

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

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

<table>
<thead>
<tr>
<th>Any anxiety disorder</th>
<th>55 (31%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Panic</td>
<td>20 (11%)</td>
</tr>
<tr>
<td>SAD</td>
<td>26 (15%)</td>
</tr>
<tr>
<td>OCD</td>
<td>17 (10%)</td>
</tr>
<tr>
<td>GAD</td>
<td>12 (7%)</td>
</tr>
<tr>
<td>PTSD</td>
<td>10 (6%)</td>
</tr>
</tbody>
</table>
The outcome of SF-36 (Mental Health)

Vitality
- Feel tired all of the time
- Feels full of pep and energy all of the time

Social-fuctioning
- Extreme interference with normal social activities
- Performs normal social activities without interference

Role-Emotional
- Problem with work or other daily activities
- No problem with work or other daily activities

Mental Health
- Feeling of nervousness and depression all of the time
- Feels peaceful, happy, and calm all of the time

* : p < 0.0001 (vs. before treatment)
Perform all types of physical activities including the most vigorous after 12 weeks administration on Paroxetine. The outcome of SF-36 (Physical Health) shows improvements in Depressed patients. Standard score (Japanese) shows the following:

- **Psyshical Functioning**: Limited a lot in performing all physical activities.
- **Role-Physical**: Problems with work or other daily activities.
- **Bodily Pain**: Very severe and extreme limiting pain.
- **General Health**: Evaluates personal health as poor and believes it is likely to get worse.

* : \( p < 0.0001 \) (vs. before treatment)
Mean score of eight SF-36 sub-scales by Paroxetine at baseline & 12 weeks after

** : vs baseline  $p<0.0001$

Vitality (VT)  Social Functioning (SF)  Role-Emotional (RE)  Mental Health (MH)  Physical Functioning (PF)  Role-Physical (RP)  Bodily Pain (BP)  Global Health Perception (GH)

N=178
Time-course change of percentage of patients who respond to paroxetine
(decrease rate of more than 50% in HAM-D total score)
Percentage of patients who remit (HAM-D is 7 or less)
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
Toshiya INADA
国立精神・神経センター
精神保健研究所

出版社：じほう
Comparison with Imipramine

Target: MDD, Depressive state

- amoxapine
- fluvoxamine
- trimipramine
- nortriptyline
- lofepramine
- paroxetine (20mg)
- sertraline (75mg)
- amitriptyline
- clomipramine
- milnacipran
- sulpiride
- paroxetine (40mg)
- trazodone
- Doxepin
- sertraline (150mg)
- mianserin
- maprotiline
- Lithium Carbonate

Relative Risk (95% CI)

imipramine is better → comparison drug is better

Comparison with Imipramine

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

- **Amitriptyline**
  - Vs paroxetine (40mg/day)

- **Imipramine**
  - Vs paroxetine (20mg/day)

- **Trazodone**

**Relative Risk (95% CI)**

Paroxetine is better  ↔  Comparison drug is better
Comparison with Fluvoxamine

Fluvoxamine is better

Comparison drug is better

Relative Risk (95% CI)

0.4  0.6  0.8  1.0  1.2  1.4

Fluvoxamine is better

comparison drug is better
In Summary

- Statistically different
  - Amoxapine > Imipramine
  - Paroxetine > Trazodone

- Overall
  - “Do-do bird verdict”

- Get more skeptical
  - Comparison with placebo
  - Comparison with psychotherapies
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
- 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

Antidepressant 12 wks

Depression

Don’t Treat

Chance Node

0.68

Rermit

0.32

Not

0.5

Rermit

0.5

Not
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.

<table>
<thead>
<tr>
<th></th>
<th>PX</th>
<th>Observe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benefit</td>
<td>Recover 0.68 x 78</td>
<td>Recover 0.5 x 78</td>
</tr>
<tr>
<td>Harm</td>
<td>Any side effects 0.64 x -20 (?)</td>
<td>Zero</td>
</tr>
<tr>
<td>Total</td>
<td>40.2</td>
<td>39</td>
</tr>
</tbody>
</table>
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

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
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/

861-1116
菊池郡合志町福原208
Tel (096) 248-2111
Fax (096) 248-4559
Phase and outcome of depressive episode

Normal

Sub-syndrome

Clinical Syndrome

Worsening to clinical disorder

Response

Remission

Relapse

Recovery

Recurrence

Treatment phase

Acute

Continuation

Maintenance