Brief history of REAP research collaboration in Asia

REAP consortium
Prepared in June 2018
Origin of REAP 1999-2001

Research on East Asia

Psychotropic Prescription Patterns

Later REAP was changed to Research on Asian Psychotropic Prescription Pattern as other Asian countries joined.
Research at Kobe University ICMR

• International Center for Medical Research (ICMR) Kobe University had been a core University to promote large scale research collaboration with Asia.
• Funded by Japan Society for Promotion of Sciences (JSPS).
• Research collaboration among leading Universities in Indonesia, Japan, Philippines, Singapore and Thailand.
Kobe University International Center for Medical Research (ICMR)
JSPS-NUS conference in 1999

International Symposium on New Challenges of Neuropsychopharmacology

Singapore National University.

December 1, 1999

Participants from Singapore, Japan and other East Asian countries.

Differences in prescribing pattern of psychotropics among participating countries were noted.
Recommendation from JSPN-NUS Conference in 1999

Interests to initiate a collaborative research to study prescription pattern of psychotropics in Asian countries.


- Prof Kua Eee Heok, Prof Tan Chay Hoon and Prof N Shinfuku discussed the plan.
Preparation of research protocole 2000-2001

- Objectives: to survey prescription of persons with mental illness in East Asia

Survey on Schizophrenic inpatients
- A unified research protocol
- Common questionnaire in 2000

- Recruitments of researchers from East Asia using the personal network.
Principles

- Unified research protocol
- Standardized assessment tools
- Agreed definition of terms and criteria
- Careful preparation and friendship
- Meetings of investigators
- Friendly criticism among researchers
- Common data inputs and analysis
- Presentation at meetings and journals.
Pilot surveys in 2000-2001

• Pilot survey (September – December 2000)
• 1st, 2nd, 3rd investigators meetings to agree on the protocol and plan of works (Kobe, Osaka and Beijing)
• Finalization of protocols and agreements on format for data entry
REAP Survey in 2001

- Survey (1st to 31st July 2001) at 6 countries.
- Persons diagnosed with schizophrenia
- Inpatients
- Data entry (Date to be sent from participating countries to Kobe coordinating center)
- 5th Investigator's meeting in Singapore in October 2001 to evaluate the data.
- The first survey was named as REAP AP 1
Objectives

1. To study psychotropic drugs utilization and their changes in Asian countries.
2. To analyze factors affecting utilization pattern of psychotropic drugs in the participating countries.
3. To suggest ways to improve prescription habits of psychotropic drugs in the participating countries.

To survey: Schizophrenic Inpatients

Inclusion criteria: ICD-10, DSM-4, CCMD
China, Hong Kong, Korea, Japan, Singapore and Taiwan participated.
Participating centers

- China: (Beijing, Shanghai, Chengdu)
- Hong Kong
- Japan: (Kobe, Kita-Kyusyu, Fukuoka, Hiroshima, Yamanashi)
- Korea: (Seoul)
- Taiwan: (Kaohsiung)
- Singapore
Presentation of the data

• 6th investigator's meeting in Kobe (February 9th 2002), ICMR Kobe University School of Medicine.

• Reports from each participating countries.

• China, Hong Kong, Indonesia, Japan, Korea, Malaysia, Singapore, Taiwan etc.

• Publication of the Proceeding of REAP
REAP AP 1 findings

- 2,398 prescription from 6 countries and areas were collected and analyzed.

- China 611 cases from Beijing, Shanghai and Chengdu.
- Hong Kong 108 cases from one hospital.
- Japan: 627 cases from 10 hospitals.
- Korea: 441 cases from 12 hospitals/clinics.
- Singapore: 300 cases from Woodbridge Hospital.
- Taiwan: 311 cases from 4 hospitals.
REAP 2001 Survey Summary

• Prescription pattern differs greatly country by country
• China uses clozapine as the first choice
• Japan has a tendency of poly-pharmacy and a prescription of the high dosage
• Singapore favors the use of depot
• Prescription habits might be influenced the licensing policy and cost rather than scientific data.
WPA Yokohama 2002

• In 2002, Japan Society of Psychiatry and Neurology organized the World Congress of Psychiatry in Yokohama.
• It was the first WPA Congress in Asia and attended by more than 6,000 participants from all over the world.
• REAP organized the Symposium at WPA and which attracted attention of participants and media.
12th World Congress of Psychiatry
Yokohama Japan August 2002
Publications

- After the REAP AP 1 survey, several papers were published using the data from the survey.
- During 2001 to 2004, around 10 papers were accepted and the publication continued at each REAP surveys.
Publications in 2003 in Japan


• The paper gave big impacts in Japan.

• Showed the first time in comparative manner
  -Highest dose of prescription
  -Polypharmacy in Japan
Publication in China in 2003

- The paper showed the unique prescription pattern in China.
- Clozapine was the first choice. Often co-prescribed with chlorpromazine. Clo-chlo combination.
- China organized a similar prescription survey in 10 provinces in China using REAP research protocol and questionnaire.
Publication in 2004

• The first English paper on REAP was published at International Journal in 2004.
High dose use and polypharmacy in 2004

- High dose antipsychotic use and polypharmacy were recognized as major challenges in East Asia.
Paper on Singapore in 2004

• Singapore used the highest rate of depot form and the combination with oral intake was prevalent.

• Two papers were published on the above topics.
Levomepromazine use in Japan

- Japan was unique in prescribing levomepromazine (LP) more often than other countries.
- Sedation of patients played an important role in pharmacotherapy in Japan.
Impacts of REAP AP in East Asia

- Increased awareness of prescription pattern of psychotropic drugs among Asian countries participated in REAP AP survey.
- High dose of antipsychotic prescription and polypharmacy were recognize as major challenges.
- Formation of friendly research network among Asian psychiatrists.
REAP Impacts in Japan.

- REAP data provided a concrete figure of high dose prescription and polypharmacy in Japan for the first time comparing with other East Asian countries.
- These data were reported by leading pharmacologists and reported by many psychiatrists in Japan.
- These data might have contributed to reduce the high dose prescription and poly-pharmacy at a late stage.

REAP AP 2 Survey in 2004

• REAP AP (2001) survey leads the follow up survey in 2004 as many researchers wished to continue a friendly research network.

• REAP AP 2: a follow up survey was carried out in 2004 to evaluate the changing trends of psychotropic prescription.
Follow up survey in 2004 Anti-psychotic drugs

- To review the change since 2001.
- Used the same research protocol
- 25 hospitals and 203 psychiatrists participated from 6 countries and areas
- China (504 cases), Hong Kong (100), Japan (583), Korea (412), Singapore (91) and Taiwan (446).
- In total 2138 cases collected as valid entry.
Changes from 2001-2004

- REAP AP 2 survey showed the changes of prescription from 2001 to 2004.
- Overall, the amount of anti-psychotics dose (CLP-equivalence) was decreased. The decreases was significant in Japan.
- A number of newer anti-psychotics were introduced in Asian countries during 2001-2004.
Mean Doses of Antipsychotics
(in CPZ equivalent means)

<table>
<thead>
<tr>
<th>Country</th>
<th>2001</th>
<th>2004</th>
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<tbody>
<tr>
<td>CHINA</td>
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<tr>
<td>H. K.</td>
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<tr>
<td>*JAPAN</td>
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<td>KOREA</td>
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<td>S'PORE</td>
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<td>TAIWAN</td>
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</table>

*p-value < 0.05*
Decrease of prescription of typical antipsychotics in Japan (REAP AP)

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<tr>
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<th>2001 July</th>
<th>2004 July</th>
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<tbody>
<tr>
<td>Haloperidol</td>
<td>48.6%</td>
<td>21.7%</td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>33.0%</td>
<td>21.4%</td>
</tr>
</tbody>
</table>
Increase of prescription of atypical antipsychotics in Japan (REAP AP)

2001 July vs 2004 July

- **Risperidone**
  - 2001: 25.5%
  - 2004: 47.2%

- **Olanzapine**
  - 2001: 5.4%
  - 2004: 22.0%

- **Quetiapine**
  - 2001: 8.6%
  - 2004: 11.8%

- **Perospiron**
  - 2001: 0.0%
  - 2004: 6.8%
REAP AP 2 papers

- Papers were published to identify changes and contributing factors to low dose and high dose prescription
REAP AD 1 Survey in 2004

- REAP on anti-depressants.
- REAP AD: Survey on prescription of anti-depressants was carried out in five countries and area.
- Five countries/regions have agreed to participate. China, Korea, Japan, Taiwan and Singapore.
Survey on antidepressants

- At several REAP symposia, requests were made to do a survey on prescription on depressive disorders since 2001.

- The survey in 2004 was called as REAP AD 1 as the follow up survey was carried out in 2012 (REAP AD 2)
Technical problems

• The difficulties were anti-depressants were prescribed for varieties of psychiatric diseases.

• Another difficulty was diagnostic criteria of mood disorders. Subjectivity.

• Target was changed from disease (depression) to drugs (anti-depressants)
REAP on anti-depressants

Survey carried out in 2004.

• The major change from REAP AP was to use anti-depressants as inclusion criteria
  - Inclusion criteria: 56 anti-depressants listed at ATC-DDD (WHO Center Oslo)
Results-Overall

- Total 1.898 samples from 20 teaching hospitals and major psychiatric institutions in East Asia were collected:
  - China (537 cases), Japan (609), Korea (293), Singapore (72), Taiwan (387). Total 1.898 samples.

This was the first large international survey to study the prescription of anti-depressants in Asia. However, there were many shortfalls in the survey, e.g.:
  - Disparity in number from participating countries/areas
  - Differences in settings where samples were collected.
Results of REAP AD 2004

• One third of prescription was made for non-mood (affective) disorders.(non-F3).
• Out of 56 anti-depressants (ATC-DDD), 26 anti-depressants were prescribed in East Asia.
• F4 neurotic, stress related and somatoform and F3 schizophrenia received anti-depressants.
• SSRI and SNRI are most commonly prescribed.
• Amitriptyline was prescribed for 6.3%.
• The prescription of anti-depressants differed greatly country by country.
Change from Tricyclic to SSRI

- SSRI and SNRI were introduced in Asia.
- Fluoxetine, sertraline, citalopram, venlafaxine were available in Asia at the time of the survey in 2004.
Japanese exception

• Exceptional situation of Japan on the use of anti-depressants was reported by Japanese psychiatrist who participated in the survey.

• Uchida N, Chong MY, Tan CH et al.: International study on antidepressant prescription pattern at 20 teaching hospitals and major psychiatric institutions in East Asia: Analysis of 1898 cases from China, Japan, Korea, Singapore and Taiwan. Psychiatry Clin Neurosci.;61(5):522-8.2007.

REAP AD findings in Japan:

- Japan had a very limited choice in 2004.
- Fluoxetine, sertraline, citalopram, venlafaxine were not available in Japan at the time of the survey.
- Extremely long drug lag.
- Government regulation to approve new drug is strict in Japan.
REAP symposium at international congress

- REAP organized a number of symposium at international congress in Asia from 2004 to 2008.
- 2002 August 12th WPA World Congress Yokohama
- 2004 October 18th WCSP (Social Psychiatry) Kobe
- 2005 CINP Regional Meeting in Beijing
- 2006 12th PRCP (Pacific Rim College) in Taipei
- 2006 REAP Mtg in Kaosiung
- 2007 WPA Regional Meeting in Seoul
- 2007 WPA Regional Meeting in Shanghai
- 2008 August 11th ASEAN Conference in Bangkok
- 2008 13th PRCP Tokyo
WPA Regional Meeting in Shanghai, September 2007
Review papers on REAP AP in 2008

- In 2008, chiefs investigators were invited to write a review paper on REAP.


REAP AP 3 in 2008

• From 2004 to 2008, several new anti-psychotropic drugs entered into clinical world in Asia.
• It was considered useful to undertake the third follow up survey in 2008.
• 2008 Thailand, Malaysia and India joined
• In total 9 countries and regions participated in the survey in 2008.
Research on Asian Psychotropic prescription study, REAP.
REAP AP-3, 2008

• REAP AP 3 survey was completed in October 2008
• Overall, 2,226 outpatients were recruited from 50 hospital psychiatric units on 9 regions: China, Korea, Japan, Taiwan, Hong Kong, Singapore, Thailand, Malaysia, and India.
• Reported at REAP symposium at the 2nd World Congress of Asian Psychiatry (WCAP) held at Taipei in November 2009.
## REAP: Distribution of subjects and country

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<td>100</td>
<td>100</td>
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<tr>
<td>Japan</td>
<td>627</td>
<td>583</td>
<td>514</td>
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<tr>
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<td>412</td>
<td>284</td>
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<td>91</td>
<td>100</td>
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<tr>
<td>Taiwan</td>
<td>311</td>
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<td>499</td>
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<td>Thailand</td>
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<td><strong>Total</strong></td>
<td><strong>2399</strong></td>
<td><strong>2136</strong></td>
<td><strong>2226</strong></td>
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# Study subjects and sites

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<tr>
<td><strong>Total</strong></td>
<td><strong>2399</strong></td>
<td><strong>2136</strong></td>
<td><strong>2226</strong></td>
<td><strong>144</strong></td>
<td><strong>204</strong></td>
<td><strong>180</strong></td>
<td><strong>31</strong></td>
<td><strong>25</strong></td>
<td><strong>34</strong></td>
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</table>
2008-on Publication

- Increased number of Publication at international and domestic journals.
- FGA and SGA
- Side effects
- Compare with other Regions.
- Pharmaco-economical analysis.
From FGA to SGA

• Three REAP surveys provided changing trends of prescription pattern in Asian countries from 2001 to 2008.

• In many countries, FGA was replaced by SGAs as the drug of first choice.

Comparison of Antipsychotics Used

*p-value < 0.05
Doses of Antipsychotics (in CPZ equivalent median*)

LAs: long-acting antipsychotics; FGAs: first-generation antipsychotics; SGAs: second-generation antipsychotics.

Mean(SD), median: 597.5 (536.4), 450.0mg
Mean Doses of Antipsychotics
（in CPZ equivalent means*）

*CHINA H. K. JAPAN KOREA S’PORE TAIWAN
2001 2004 2008

Mean Doses of Antipsychotics

*p-value<0.05
Adjunctive treatment


Contributions by young psychiatrists

- Dr Xiang Yu Tao joined the survey from 2010 and published more than 20 papers at International journals based on REAP data.
- He made fine analysis on different aspects of psychotropic drug use.
- Xiang YT, Wang CY, Si TM etc The low frequency of reported sexual dysfunction in Asian patients with schizophrenia (2001-2009): low occurrence or ignored side effect? Hum Psychopharmacol.
Clozapine use in Asia

• Clozapine was the first choice in China at the REAP 1 survey in 2001. However, the use decreased from 2001 to 2009.

• The use of clozapine among Asian countries differed greatly. Clozapine was not available in Japan at 2009 survey.

Side effects

• From 2001 to 2009, SGA replaced FGA in Asia as main stream of anti-psychotics to persons with schizophrenia. This changed the profiles of side effects.


Ignored side effects in Asia


The frequency of adverse effects according to SGA usages

<table>
<thead>
<tr>
<th>Year</th>
<th>Total</th>
<th>Movement</th>
<th>Autonomic</th>
<th>Endocrine</th>
<th>Metabolic</th>
<th>Cardiovascular</th>
<th>Sedation</th>
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<tbody>
<tr>
<td>2001</td>
<td>65.8</td>
<td>28.2</td>
<td>53.8</td>
<td>1.9</td>
<td>1.9</td>
<td>0.0</td>
<td>0.0</td>
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<tr>
<td>2004</td>
<td>73.5</td>
<td>37.2</td>
<td>61.2</td>
<td>5.4</td>
<td>12.7</td>
<td>0.9</td>
<td>3.2</td>
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<tr>
<td>2008</td>
<td>70.7</td>
<td>25.2</td>
<td>57.9</td>
<td>3.9</td>
<td>16.3</td>
<td>1.4</td>
<td>3.9</td>
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</tbody>
</table>
Reported adverse events
(focus on antipsychotics)

- Over sedation*
- Cardiovascular*
- Metabolic*
- Endocrinological*
- Autonomic*
- Movement

*p value < 0.001
Use of ECT in Asia

• ECT was often used in Asia in particular in countries with limited psychiatric resource.
• The paper first described the actual prevalence of the use of ECT at clinical settings in different countries.
• Xiang YT, Ungvari GS, Correll CU etc :
REAP AD 2 in 2012

- REAP AD was carried out in 2004 with the participation of China, Korea, Japan, Taiwan and Singapore.
- The follow-up survey of REAP-AD was organized in 2012 using the similar format.
- 10 countries and areas in Asia participated.
REAP AD-2

• Data collected, March to May 2013.
• Analysis completed, July 2013
• In total 2,320 cases from 10 countries
• 40 centers
• 215 psychiatrists
• China (350), Indonesia (269), Hong Kong (81), Japan (246), Korea (259), Singapore (135), Taiwan (199), India (309), Malaysia (161) and Thailand (311).
REAP-AD 2, 2013

• Cross-sectional, Drug-centered survey

• Date of the survey: the first March 2013

• Participating countries and area:
  • 10 countries
    China, Hong Kong, Korea, Japan, Taiwan, Singapore, Malaysia, Thailand, India, Indonesia
Methods

• Inclusion criteria

Patients who are receiving antidepressant medications (62 agents classified as antidepressants in ATC-DDDs) on the day of survey.

not limited to the diagnosis of ‘depression’
REAP members meeting at PRCP September 2012 Seoul
Papers based on REAP AD 2

A number of papers was published based on the survey of REAP AD 2.

• The papers included pattern of anti-depressants prescription in Asia, side effects, co-morbidity, suicidal thoughts.

• The comprehensive paper was published by Hong Kong team

Paper from Malaysian colleague

- Chee KY, Tripathi A, Avasthi A etc:

- REAP encouraged young Asian psychiatrists to joined REAP and contributed to publication.
4th WCAP Bangkok in 2013
REAP paper from Malaysia
Paper from Korean colleague

- Korean centers actively participated in the survey and several papers were published by Korean colleagues.
- Park SC, Shinfuku N, Maramis MM etc.: Adjunctive Antipsychotic Prescriptions for Outpatients with Depressive Disorders in Asia: The Research on Asian Psychotropic Prescription Patterns for Antidepressants (REAP-AD) Study.
Gender difference and depression

Papers from Indian colleagues

- India joined REAP from REAP AD 2 survey in 2012 and supported REAP surveys.
3rd As CINP 2013 Beijing
Presenters at REAP symposium
REAP Members with Prof Sartorius
REAP AP 4 in 2016

- Asian Federation of Psychiatric Association (AFPA) was established in 2007.
- The formation of AFPA contributed to promote active interaction in research among Asian psychiatrists from the whole regions.
- New member countries wished to join REAP survey in 2016.
- 15 countries and areas joined the survey.
REAP group Meeting
in 2005 Fukuoka 5th WCAP
REAP Dinner, November 2015
Taipei
REAP AP 4 Survey in 2016

- Protocol and questionnaire were prepared to undertake the follow up survey of previous surveys of REAP.
- The duration was from March to June 2016.
- Many centers experienced the hardships to get the approval from Internal Review Board (IRB).
- Members were asked to get the informed consent from the participating patients.
Review of REAP AP 4 data
September 2016, Taipei
REAP AP 4 Results

• 3,742 cases were collected from 61 leading psychiatric centers of 15 countries in Asia.
• East Asia : China (160), Korea (131), Japan (229), Hong Kong (31), Taiwan (404)
• South East Asia : Singapore (171), Thailand (322), Malaysia (305), Indonesia (561), Vietnam (274), Myanmar (164)
• South Asia : India (479), Bangladesh (99), Sri Lanka (97), Pakistan (299)
<table>
<thead>
<tr>
<th>Area</th>
<th>n</th>
<th>(%)</th>
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<tbody>
<tr>
<td>Thailand</td>
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<td>18.4</td>
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<tr>
<td><strong>總和</strong></td>
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<table>
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<th>Area</th>
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<tr>
<td><strong>總和</strong></td>
<td>1997</td>
<td>100.0</td>
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Long-Form: BPRS, DIEPSS, Comorbidity, Laboratory
REAP Meeting at Pre-PRCP
2016 Nov 2\textsuperscript{nd}, Kaohsiung
Symposium of REAP AP4
17th PRCP Nov 3-5 2016 Kaohsiung, Taiwan
REAP gathering at 17th PRCP
Nov.3-5, 2016, Kaohsiung, Taiwan
REAP AP 4 Summary paper

- Shu-Yu Yang, Lian - Yu Chen, Shih - Ku Lin etc.: Polypharmacy and psychotropic drug loading in patients with schizophrenia in Asian countries: The REAP - AP4 study:
- Psychiatry and clinical neurosciences (PCN) : 14 May 2018 [https://doi.org/10.1111/pcn.12676](https://doi.org/10.1111/pcn.12676)
- Comprehensive information on prescription of psychotropic drugs in 15 countries and areas of Asia.
- Increasing trends of polypharmacy in China and Korea.
Comparison of polypharmacy rates from the REAP-AP1 to REAP-AP4.
Defined daily dose

- Shih-Ku Lin, Yen-Feng Lin, Shu-Yu Yang etc.: Comparison of the Defined Daily Dose and Chlorpromazine Equivalent Methods in Antipsychotic Drug Utilization in Six Asian Countries:
  - *Neuropsychiatry (London)* (2018) 8(2), 739–744
  - The pooled data from REAP surveys demonstrated the usefulness of DDD for the measurements of drug dose.
  - Total psychotropic drug loading in 15 countries showed the big difference among countries.
  - Japan recorded the highest psychototropic drug loading.
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Figure 1. Comparison of psychotropic drug loading between countries.
AsCSR 2017, Sept, Bangkok
Members from South Asia and West Asia joined
REAP dinner table shared by member from China, HK, Japan and Taiwan
REAP AP 4 paper from Pakistan

• We consider it important for REAP to stimulate the research minds among psychiatrists in developing countries.


• More than Half of Patients with Schizophrenia Are Receiving Polypharmacy and Co-Prescription of Anxiolytics in Pakistan — Findings from Research on Asian Prescription Pattern in 2016

• Open Journal of Psychiatry, 8, 199-211. June 8, 2018

• https://doi.org/10.4236/ojpsych.2018.83018
REAP as ongoing project

- REAP started in 2001, continued more than 18 years.
- REAP AP 4 survey in 2016 studied the prescription of 3744 persons with schizophrenia in Asia
- 486 psychiatrists from 71 psychiatric hospitals and major research institutes joined
- 15 countries and areas covering East Asia, Southeast Asia, South Asia, West Asia participated.
# REAP-AP1234

## Study subjects and sites

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Geography

- East Asia
- ASEAN
- South Asia
- Central Asia
- West Asia
Mid-Summary in 2018

- REAP is well known among Asian psychiatrists.
- In total more than 10,000 prescription of persons with schizophrenia and depression in Asia were collected and analyzed.
- More than 70 papers based on REAP survey accepted by International Journals
- REAP has become the longest and the largest international collaborative research in psychiatry in Asia.
REAP AD and REAP CV

• In 2018, we plan to undertake two international surveys.
• One is REAP survey on bipolar disorders (REAP BD) cum REAP survey on Mood Stabilizer (REAP MS).
• Another REAP survey on polypharmacy using case vignette (REAP CV).
Thank you for your continuous support

Research on Asian Psychototropic Prescription Pattern (REAP)

http://reap.asia/