Piano theory & Order dependency for MDD

1

For recovery from Mood disorders

Itsuo Asai MD.

COI

- We have no COI to disclose in connection with this presentation.

Content

- **Let's review STAR-D.**
- **What is Piano theory?**
- **What is Order Dependence**
  in the Treatment Process for Depression?
- Unresolved question:
  where does Loss of energy come from?
  Central or Peripheral?

STAR-D brought us what?

Let's review STAR-D.

Citalopram monoSSRI complete remission 28–33%

- Other SSRI or Citaroplam+ CBT showed almost same results

National Institute of Mental Health. *Sequenced Treatment Alternatives to Relieve Depression (STAR*D) Study.* [Accessed March 12, 2012]. Available from: http://www.nimh.nih.gov/trials/practical/stard/index.shtml.

Desperation for antidepressant treatment of MDD was prevailed world wide.

Let's take a closer look at the STAR-D results

What STAR D showed does not necessarily indicate that the monoamine adjustments are invalid.

National Institute of Mental Health. *Sequenced Treatment Alternatives to Relieve Depression (STAR*D) Study.* [Accessed March 12, 2012]. Available from: http://www.nimh.nih.gov/trials/practical/stard/index.shtml.

1）Citalopram monoSSRI complete remission 28-33%

- Other SSRI or Citaroplam+ CBT showed almost same results

2）+miltazapin, + nortoriptylin40.3%-45.3%. 47.8%-52.8%

3）+triiodothyronine, +lithium 43.9%-52.9%, 52.7%-57.7%

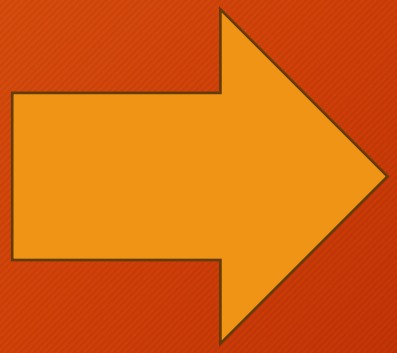
4）2)3)+tranylcypromine,+venlafaxine 56.9%-70.7%

The sequenced treatment alternatives to relieve depression (STAR*D) trial: a r

Mark Sinyor[1], Ayal Schaffer, Anthony

What do the STAR-D results lead us to?

- Citalopram,+Mirtazapine, Triiodothyronine, +Venlafaxine
- = Serotonergic agent + Noradrenergic agent

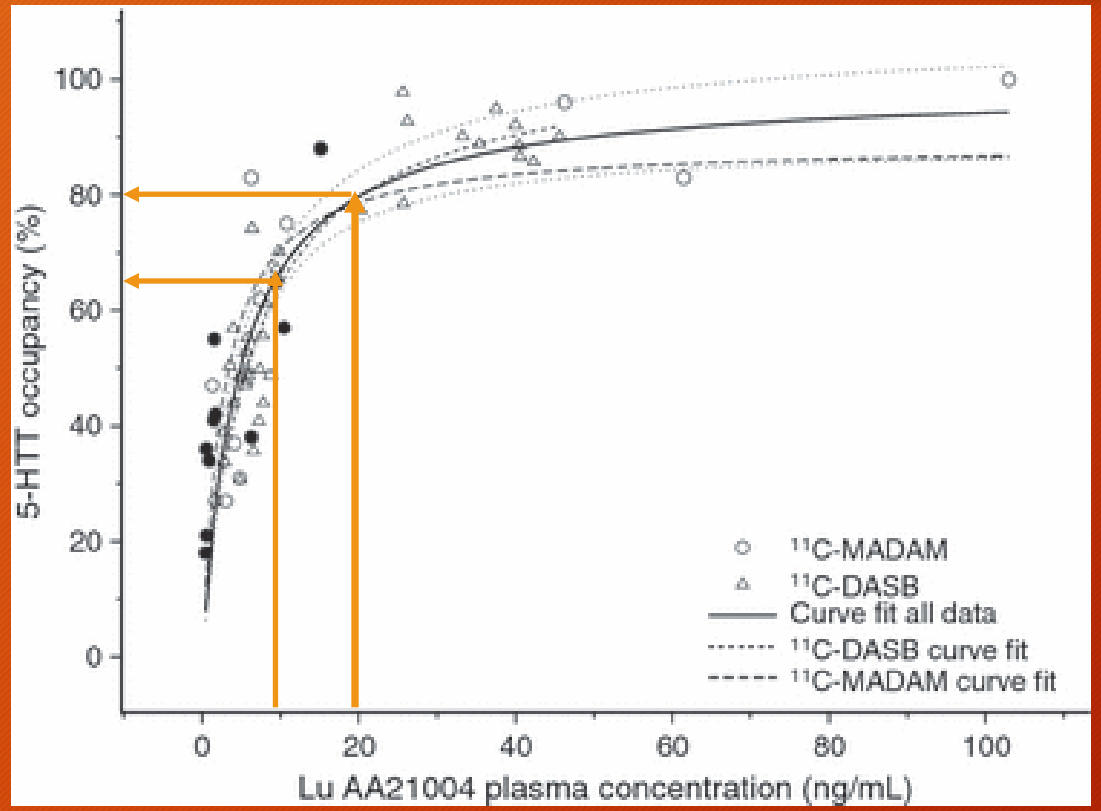


56.9%–70.7%

Sufficient doses are needed to get remission

- It may be necessary to use antidepressants in sufficient doses to achieve complete remission for around 56.9-70% patients.

20mg of Vortioxetine is needed to get to 80% occupancy of 5HT receptors in Raphe



Occupancy of the Serotonin Transporter after Administration of Lu AA21004 and its Relation to Plasma Concentration in Healthy Subjects

Basic Clin Pharma Tox, Volume: 110, Issue: 4, Pages: 401-404, First published: 10 October 2011

Is it true 80% is enough for antidepressant?

STAR-D gives us the result,

- With **sufficient amounts of serotonin and noradrenaline, 56.9-70%** may have a complete remission.(escitlopram+venlaphaxine+miltazapine)

Caution!!
Three-drug administration is not covered by insurance. Please deal with this in another way.

Perhaps the order has something to do with it?

- In STAR-D, serotonergic agents are administered followed by noradrenergic agents, which have produced these results. Many noradrenergic agents that have only a single noradrenergic effect (e.g., Atomoxetine) have not been shown to be effective as antidepressants. This may be due to the fact that serotonergic agents are not administered first or simultaneously.

New theories for MDD, beyond monoamine hypothesis

1. The neuroplasticity theory
2. The neurogenesis theory

• . 2018 Jan;72(1):3-12.
doi: 10.1111/pcn.12604. Epub 2017 Oct 19.

Neural basis of major depressive disorder: Beyond monoamine hypo

Shuken Boku[1], Shin Nakagawa[2], Hiroyuki Toda[3], Akitoyo Hishimoto[1]
Affiliations
•PMID: 28926161
•DOI: 10.1111/pcn.12604

Major problems for the monoamine hypothesis

- the most serious problem of the monoamine hypothesis is that **it fails to explain why antidepressants have the latency of response; if antidepressants work based on the monoamine hypothesis, they are considered to be rapidly effective**.[3]

•2018 Jan;72(1):3-12. doi: 10.1111/pcn.12604. Epub 2017 Oct 19.

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- Miltazapine seems to be rapidly effective.
- Duloxetin seems to be just a bit slowly effective than Miltazapin.
- Other SSRIs seems to be slowly effective than the medicines above.
- It may only because it needs time to get to the necessary concentration level of monoamine to be effective. After getting to the required concentration level in CSF the effect of the antidepressant shows up immediately.

I bid Jan. 3rd 2022

Use of sufficient quantities of medicine

- Although other ways to ameliorate the abnormal activity of microglia due to stress-induced cytokines entering the BBB, which may be the etiological factor, and the damage to the neuronal nuclei in the brain due to cortisol excess need to be explored*, at this point, **for us psychiatric clinicians, we need to first make good use of existing drugs. It seems to me that the first step is to make good use of existing drugs.**

*Jiang J, Yang M, Tian M, Chen Z, Xiao L, Gong Y. Intertwined associations between oxytocin, immune system and major depressive disorder. Biomed Pharmacother. 2023 Jul;163:114852. doi: 10.1016/j.biopha.2023.114852. Epub 2023 May 8. PMID: 37163778; PMCID: PMC10165244.

Major problems for the monoamine hypothesis

up to 30% of patients with MDD are refractory to currently used antidepressants.

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What about for the remaining 30-44%?

- New therapeutic agents are needed, preferably of substances that are appropriate to the etiology, but in clinical practice there is no choice but to use existing agents.

- Lithium?

In the acute-treatment trials, the average response rate in the lithium group was 45%, and in the placebo group, 18% ($P < 0.001$).

Bauer M, Adli M, Baethge C, Berghöfer A, Sasse J, Heinz A, Bschor T. Lithium augmentation therapy in refractory depression: clinical evidence and neurobiological mechanisms. Can J Psychiatry. 2003 Aug;48(7):440-8. doi: 10.1177/070674370304800703. PMID: 12971013.

- Xiong Y, Karlsson R, Song J, Kowalec K, Rück C, Sigström R, Jonsson L, Clements CC, Andersson E, Boberg J, Lewis CM, Sullivan PF, Landén M, Lu Y. Polygenic risk scores of lithium response and treatment resistance in major depressive disorder. Transl Psychiatry. 2023 Sep 28;13(1):301. doi: 10.1038/s41398-023-02602-3. PMID: 37770441; PMCID: PMC10539379.

When to use lithium?

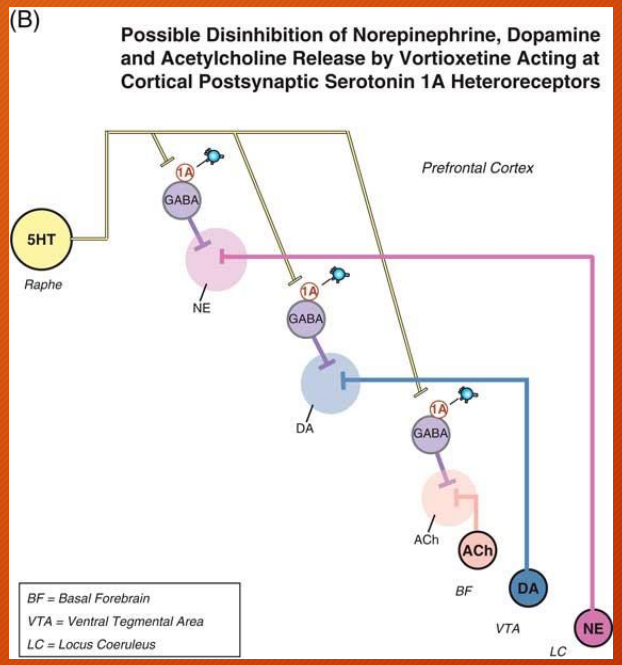
Lithium is more effective for Treatment Resistance Depression after receiving ECT.

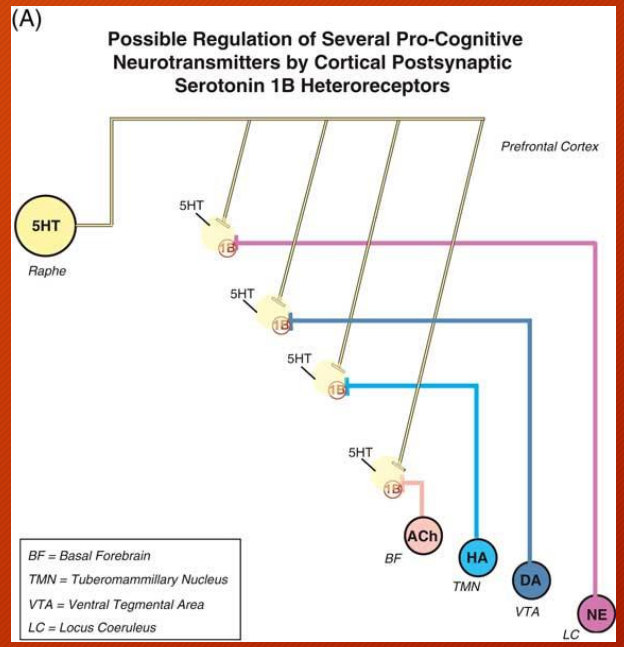
Definition	Sample sizes		Antidepressants response			Lithium response		
	TRD	non-TRD	Mean difference in $PRS_{standardized}$	*P*	P_{FDR}	Mean difference in $PRS_{standardized}$	*P*	P_{FDR}
Broad	1778	2264	−0.015	0.631	0.794	0.094	0.003	0.012*
Narrow_1	1487	1483	−0.010	0.794	0.794	0.107	0.004	0.012*
Narrow_2	1081	1483	0.013	0.742	0.794	0.104	0.009	0.018*

- Xiong Y, Karlsson R, Song J, Kowalec K, Rück C, Sigström R, Jonsson L, Clements CC, Andersson E, Boberg J, Lewis CM, Sullivan PF, Landén M, Lu Y. Polygenic risk scores of lithium response and treatment resistance in major depressive disorder. Transl Psychiatry. 2023 Sep 28;13(1):301. doi: 10.1038/s41398-023-02602-3. PMID: 37770441; PMCID: PMC10539379.

Vortioxetine; Serotonin Cascade Hypothesis.

Remnants of the serotonin hypothesis.





Modes and nodes explain the mechanism of action of vortioxetine, a multimodal agent (MMA): actions at serotonin receptors may enhance downstream release of four pro-cognitive neurotransmitters

Published online by Cambridge University Press: 11 June 2015

Stephen M. Stahl

Piano theory

21

Definition, Functions and its Future

Heart Clinic Itsuo Asai MD.

Piano Theory, What is?

- Receptors in the neuronal nucleus may operate by turning on or off a single receptor, but many operate by a combination of turning on and off multiple types of receptors.
  - This means that disorders with complex pathophysiology, such as MDD, need to be treated by considering on/off combinations of multiple types of receptors.
- Ex, **HT1A on, TH1B 50%on, HT3, 7 off, HT1D of, serotonin transporter off, Noradrenalin alfa 1B on, …** profile of vortioxetine

Vortioxetine: Clinical Pharmacokinetics and Drug Interactions

Grace Chen,1 Astrid-Maria Højer,2 Johan Areberg,2 and George Nomikos3

Clin Pharmacokinet. 2018; 57(6): 673–686. Published online 2017 Nov 30.

- They may be activated by a single neurotransmitter, but often by a combination of multiple neurotransmitters.
  - That in order to treat a complex pathological disorder such as depression, it is necessary to consider not serotonin alone, but in combination with other neurotransmitters such as noradrenaline and dopamine, BDNF…

Piano theory, What for?

1)It may help you to explain the outlook for the course of your treatment.
2)The order of medicines to be used is determined theoretically
3)You may be able to give instructions on the appropriate attitude of patients for their treatment at the appropriate time
4)You may be able to clearly classify and define TDRs.
(It may be easier to envision which parts of the brain's neurona nuclei and neural pathways are most noticeably damaged).

Piano theory, for future

- The new issue is,
- **1) Establishing proof that neurotransmitter changes (Transmitter Switch) are occurring, i.e., order dependency. You may be able to see the neurotransmitter switch in your office with your clients.**
- **2) The new challenge is to clarify the combination of related receptors and the order in which they are approached.**

Related to 1) Li HQ, Jiang W, Ling L, Gupta V, Chen C, Pratelli M, Godavarthi SK, Spitzer NC. Generalized fear following acute stress is caused by change in co-transmitter identity of serotonergic neurons. bioRxiv [Preprint]. 2023 May 11:2023.

Order dependency

25

Definition, neurocircuits and evidence

Order dependency in the treatment for MDD

- **In the treatment for depression,**
  - 1) Sadness, anger, anxiety, autonomic symptoms, sleep disturbances
  - 2) guilty feeling , impaired thinking, executive dysfunction, suicidal ideation, depressed mood,
  - 3) Tiredness
  - 4) More tired than usual
  - 5) lack of energy
  - 6) Sleep disturbances

- In particular, if 1) does not fade away or at lease reduced in some degree, 2) is less likely to fade away, and if 1) and 2) do not fade away or at least reduced in some degree, 4) tends to be less likely to be improved, thus there may be an order dependence in the treatment of depression.

Evidence for order dependency is now scarce but Might be easily obtainable.

- **Objective**; to verify order dependency for treatment of MDD
- **Method**; We surveyed 105 patients(mean age58.9yrs, male53,female52) with DSM-5TR diagnosis of major depressive disorder who visited the Heart Clinic from November 1 to 31, 2023 for 3 months. The patient group was limited to those with no comorbidities other than depression.
- **Results**; The number of those that followed the Order dependency during the course of the study was 102 and 3 who did not.(97.1% of patients were not out of Order Dependency. Complete remission54.2%, Remission61.9%,Response90.5%, non-Response9.5%)
- **Discussion**; Although the study showed that in patients who met the diagnostic criteria for major depressive disorder in the DSM-5TR and had no comorbidities, their treatment process almost met Order dependency, a larger study is needed to authenticate it as a general fact because it was a study of a relatively small number of cases and a single institution.

Neurocircuit as suggested by Order Dependency

- **Excitation of amygdala by thalamic and hypothalamic inputs can be assumed to be located above serotonergic circuits in the ACC region and Raphe nucleus.**
- **The serotonergic circuits in the Raphe nucleus and ACC regions may be located above the noradrenergic circuits in the locus coeruleus and others, as well as above the injured unknown region that causes the symptoms of described as loss of energy.**

Complete form of Piano Theory

- By turning on and off the piano keys, or receptors, like a pianist playing in a certain order, sometimes with several receptors simultaneously and sometimes alone, the symptoms of depression disappear, i.e., complete remission may be able to be achieved.

Heart Clinic Itsuo Asai MD.

From the perspective of Piano Theory and Order dependency

What is TRD?

Many symptoms that remain are lack of energy

- Noradrenergic drugs often fail to diminish the symptoms.(on our data, unpublished)
- What is perceived as physical loss may be peripheral. This may be related to abnormalities in the postural holding muscles due to faulty cortisol receptors.
- For central abnormalities, other substances may be involved.

New treatment but within the old framework

Single-Dose Psilocybin Treatment for Major Depressive Disorder

for a treatment-resistant episode of major depression

Raison CL, Sanacora G, Woolley J, Heinzerling K, Dunlop BW, Brown RT, Kakar R, Hassman M, Trivedi RH, Robison R, Gukasyan N, Nayak SM, Hu X, O'Donnell KC, Kelmendi B, Sloshower J, Penn AD, Bradley E, Kelly DF, Mletzko T, Nicholas CR, Hutson PR, Tarpley G, Utzinger M, Lenoch K, Warchol K, Gapasin T, Davis MC, Nelson-Douthit C, Wilson S, Brown C, Linton W, Ross S, Griffiths RR. Single-Dose Psilocybin Treatment for Major Depressive Disorder: A Randomized Clinical Trial. JAMA. 2023 Sep 5;330(9):843-853.

Goodwin GM, Aaronson ST, Alvarez O, Atli M, Bennett JC, Croal M, DeBattista C, Dunlop BW, Feifel D, Hellerstein DJ, Husain MI, Kelly JR, Lennard-Jones MR, Licht RW, Marwood L, Mistry S, Páleníček T, Pedjon O, Repantis D, Schoevers RA, Septimus B, Simmons HJ, Soares JC, Somers M, Stansfield SC, Stuart JR, Tadley HH, Thiara NK, Tsai J, Wahba M, Williams S, Winzer RI, Young AH, Young MB, Zisook S, Malievskaia E. Single-dose psilocybin for a treatment-resistant episode of major depression: Impact on patient-reported depression severity, anxiety, function, and quality of life. J Affect Disord. 2023 Apr 14;327:120-127.

Single-Dose Psilocybin Treatment for Major Depressive Disorder

eTable 2: Sensitivity Analyses for Montgomery Asberg Depression Rating Scale (MADRS) Score at Day 43 and Day 8 – Intent to Treat (ITT) Population

	Psilocybin (N=51)	Niacin (N=53)	MMRM Analysis[a]	
Study Visit/Statistic	n	n	LS Mean Difference (SE) [95% CI]	P-value[c]
Primary Endpoint: Post-Dose Day 43 Change from Baseline				
MAR Multiple Imputation[b]	51	53	-12.6 (2.6) [-17.7, -7.5]	<.001
Key Secondary Endpoint: Post-Dose Day 8 Change from Baseline				
MAR Multiple Imputation[b]	51	53	-12.1 (2.3) [-16.6, -7.6]	<.001

Notes: N = number of participants in ITT Population, stratified by randomized treatment group; n = number of participants with complete or imputed MADRS assessment at study visit. LS = Least Squares; SE = Standard Error; NA = Not applicable.
Note that two additional imputation analyses were prespecified to be performed (see supplemental methods eAppendix eTable 2) but no participants in the psilocybin group had missing data due to lack of efficacy, so the additional imputation analyses were not run.
[a] Least squares means differences and p-value from MMRM model adjusted for baseline score, site, sex and treatment resistant depression. Rubin's Rule used to combine estimates across imputed datasets (Rubin, 1987).
[b] All missing MADRS scores imputed using MCMC method to create 50 completed datasets.
[c] P-values not corrected for multiple comparisons.

Raison CL, Sanacora G, Woolley J, Heinzerling K, Dunlop BW, Brown RT, Kakar R, Hassman M, Trivedi RP, Robison R, Gukasyan N, Nayak SM, Hu X, O'Donnell KC, Kelmendi B, Sloshower J, Penn AD, Bradley E, Kelly DF, Mletzko T, Nicholas CR, Hutson PR, Tarpley G, Utzinger M, Lenoch K, Warchol K, Gapasin T, Davis MC, Nelson-Douthit C, Wilson S, Brown C, Linton W, Ross S, Griffiths RR. Single-Dose Psilocybin Treatment for Major Depressive Disorder: A Randomized Clinical Trial. JAMA. 2023 Sep 5;330(9):843-853

Single-Dose Psilocybin Treatment for Major Depressive Disorder

eTable 3: Depressive Symptom Response and Remission by Study Visit and Randomized Treatment Group – Intent to Treat (ITT) Population

	Psilocybin			Niacin		
Outcome/Study Visit	**N**	**n (%)**	**95% CI[b]**	**N**	**n (%)**	**95% CI[b]**
Depressive Symptom Response[b]						
Post-Dose Day 8	51	27 (53)	38.5, 67.1	50	5 (10)	3.3, 21.8
Post-Dose Day 15	50	25 (50)	35.5, 64.5	45	8 (18)	8.0, 32.1
Post-Dose Day 29	49	26 (53)	38.3, 67.5	44	7 (16)	6.6, 30.1
Post-Dose Day 43	50	29 (58)	43.2, 71.8	44	9 (20)	9.8, 35.3
Depressive Symptom Remission[c]						
Post-Dose Day 8	51	18 (35)	22.4, 49.9	50	4 (8)	2.2, 19.2
Post-Dose Day 15	50	20 (40)	26.4, 54.8	45	6 (13)	5.1, 26.8
Post-Dose Day 29	49	18 (37)	23.4, 51.7	44	5 (11)	3.8, 24.6
Post-Dose Day 43	50	22 (44)	30.0, 58.7	44	5 (11)	3.8, 24.6

Notes: N = number of participants in ITT Population completing Montgomery Asberg Depression Rating Scale (MADRS) assessment at study visit, stratified by randomized treatment group; n = number of participants meeting the definition for depressive symptom response or depressive symptom remission at study visit.
[a] 95% Confidence Intervals are from an exact binomial distribution (Clopper-Pearson).
[b] Depressive symptom response is defined as a ≥ 50% reduction from Baseline central-rater MADRS total score at post-dose assessment.
[d] Depressive symptom remission is defined as a central-rater MADRS total score ≤ 10 at post-dose assessment.

Our clinical data
Response rate
90.5%
Remission
61.9%
Complete remission
54.2%

Nov.1,2023-Jan.31,2024

Raison CL, Sanacora G, Woolley J, Heinzerling K, Dunlop BW, Brown RT, Kakar R, Hassman M, Trivedi RP, Robison R, Gukasyan N, Nayak SM, Hu X, O'Donnell KC, Kelmendi B, Sloshower J, Penn AD, Bradley E, Kelly DF, Mletzko T, Nicholas CR, Hutson PR, Tarpley G, Utzinger M, Lenoch K, Warchol K, Gapasin T, Davis MC, Nelson-Douthit C, Wilson S, Brown C, Linton W, Ross S, Griffiths RR. Single-Dose Psilocybin Treatment for Major Depressive Disorder: A

What do you think of the result ?

Wouldn't a 58% response rate and a 44% remission rate be worse than the traditional STAR-D results?

自殺予防を初め様々な臨床的トピックスが予定されております。是非とも皆様ご参加下さい。

Thank you very much for your attention.

Please come and join our world congress in Sep.25th-28th in Tokyo

PRCP&WACP2025 Joint Congress Tokyo

Itsuo Asai MD.