

【留学先】 Department of Psychiatry, University of Toronto; Centre for Addiction and Mental Health (CAMH)

【留学期間】 平成24年5月1日より平成29年3月3日まで

【指導者】 Gary Remington

【研究テーマ】 統合失調症における抗精神病薬治療の最適化

【主な研究内容】

① 抗精神病薬の投与回数：

- ・ ペルフェナジン、リスペリドン、オランザピンについて、1日1回投与と1日2回投与のどちらが臨床転帰において優れているか、CATIE 研究を解析した。
- ・ クロザピンについて、1日1回投与が行われている頻度およびその予測因子について、多施設共同横断研究を行った。
- ・ クロザピンについて、1日1回投与と1日2回投与のどちらが臨床転帰において優れているか、二重盲検無作為化比較試験を現在実施中である。

② 抗精神病薬の変更方法：

- ・ クロザピンに変更する際、前薬の急速中止と緩徐中止のどちらが臨床転帰において優れているか、二重盲検無作為化比較試験を行った。
- ・ 抗精神病薬を変更する際、前薬の急速中止と緩徐中止のどちらが臨床転帰において優れているか、無作為化比較試験のメタアナリシスを行った。
- ・ 抗精神病薬を変更する際、前薬の緩徐中止と待機後緩徐中止のどちらが臨床転帰において優れているか、無作為化比較試験のメタアナリシスを行った。
- ・ 抗精神病薬を変更する際、後薬の急速開始と緩徐開始のどちらが臨床転帰において優れているか、無作為化比較試験のメタアナリシスを行った。

③ その他：

- ・ 精神病における5症状ドメインについての簡便な評価尺度 (Brief Evaluation of Psychosis Symptom Domains (BE-PSD)) を作成し、妥当性と信頼性を検証する横断研究を行った。
- ・ 安定した統合失調症において抗精神病薬の継続と中止のどちらが全般的症状スコアの推移において優れているか、無作為化比較試験のメタアナリシスを行った。
- ・ アリピプラゾールは精神病症状を悪化させるか、症例報告のシステマティック・レビューを行った。
- ・ アリピプラゾールは精神病症状を悪化させるか、二重盲検無作為化比較試験のメタアナリシスを行った。

【公表論文】

<査読あり英文学術誌> (*責任著者)

1. *Takeuchi H, Remington G. A systematic review of reported cases involving psychotic symptoms worsened by aripiprazole in schizophrenia or schizoaffective disorder. *Psychopharmacology*. 228: 175-85; 2013
2. Nakajima S, Gerretsen P, Takeuchi H, Caravaggio F, Chow T, Le Foll B, Mulsant B, Pollock B, Graff-Guerrero A. The potential role of dopamine D3 receptor neurotransmission in cognition. *Eur Neuropsychopharmacology*. 23: 799-813; 2013
3. *Takeuchi H, Suzuki T, Remington G, Bies RR, Abe T, Graff-Guerrero A, Watanabe K, Mimura M, Uchida H. Effects of risperidone and olanzapine dose reduction on cognitive function in stable patients with schizophrenia: An open-label, randomized, controlled, pilot study. *Schizophrenia Bulletin*. 39: 993-8; 2013
4. Ishida T, Katagiri T, Uchida H, Takeuchi H, Sakurai H, Watanabe K, Mimura M. Incidence of deep vein thrombosis in restrained psychiatric patients. *Psychosomatics*. 55: 69-75; 2014
5. *Takeuchi H, Suzuki T, Bies RR, Remington G, Mamo DC, Pollock BG, Mimura M, Uchida H. Estimated dopamine D2 receptor occupancy from plasma concentrations of atypical antipsychotics and subjective experience/drug attitude in schizophrenia: An analysis of the CATIE data. *Schizophrenia Research*. 150: 373-9; 2013
6. Fervaha G, Agid O, Takeuchi H, Foussias G, Remington G. Life satisfaction among individuals with schizophrenia in the Clinical Antipsychotic Trial of Intervention Effectiveness (CATIE) study. *American Journal of Psychiatry*. 170: 1061-2; 2013
7. *Takeuchi H, Fervaha G, Uchida H, Suzuki T, Bies RR, Grönte D, Remington G. Impact of once vs. twice daily perphenazine dosing on clinical outcomes: An analysis of the CATIE data. *Journal of Clinical Psychiatry*. 75: 506-11; 2014
8. Remington G, Foussias G, Agid O, Fervaha G, Takeuchi H, Hahn M. The neurobiology of relapse in schizophrenia. *Schizophrenia Research*. 152: 381-90; 2014
9. Fervaha G, Agid O, Takeuchi H, Foussias G, Remington G. Clinical determinants of life satisfaction in chronic schizophrenia: Data from the CATIE study. *Schizophrenia Research*. 151: 203-8; 2013
10. Mizushima J, Sakurai H, Mizuno Y, Shinfuku M, Tani H, Yoshida K, Ozawa C, Serizawa A, Koide S, Kodashiro N, Minamisawa A, Mutsumoto E, Nagai N, Noda S, Tachino G, Takahashi T, Takeuchi H, Kikuchi T, Uchida H, Watanabe K, Kocha H, Mimura M. Melancholic and reactive depression: A reappraisal of old categories. *BMC Psychiatry*. 13: 311; 2013
11. *Takeuchi H, Suzuki T, Remington G, Watanabe K, Mimura M, Uchida H. Lack of Effect of risperidone or olanzapine dose reduction on metabolic parameters, prolactin, and QTc interval in stable patients with schizophrenia. *Journal of Clinical Psychopharmacology*. 34: 517-20; 2014
12. *Takeuchi H, Suzuki T, Bies RR, Remington G, Watanabe K, Mimura M, Uchida H. Dose reduction of risperidone or olanzapine and estimated dopamine D2 receptor occupancy in stable patients with schizophrenia: Findings from an open-label, randomized, controlled study. *Journal of Clinical Psychiatry*. 75: 1209-14; 2014
13. Fervaha G, Agid O, Takeuchi H, Foussias G, Remington G. Effect of antipsychotic medication on overall life satisfaction among individuals with chronic schizophrenia: Findings from the NIMH CATIE study. *European*

Neuropsychopharmacology. 24: 1078-85; 2014

14. *Takeuchi H, Suzuki T, Remington G, Watanabe K, Mimura M, Uchida H. Lack of effect of risperidone or olanzapine dose reduction on subjective experiences in stable patients with schizophrenia. *Psychiatry Research*. 15: 218; 244-6; 2014
15. Fervaha G, Takeuchi H, Agid O, Lee J, Foussias G, Remington G. Determinants of patient-rated and clinician-rated illness severity in schizophrenia. *Journal of Clinical Psychiatry*. 76: 924-30; 2015
16. Suzuki T, Uchida H, Takeuchi H, Tsuboi T, Hirano J, Mimura M. A review on schizophrenia and relapse: A quest for user-friendly psychopharmacotherapy. *Human Psychopharmacology*. 29: 414-26; 2014
17. Lee J, Takeuchi H, Fervaha G, Bhaloo A, Powell V, Remington G. Relationship between clinical improvement and functional gains with clozapine in schizophrenia. *European Neuropsychopharmacology*. 24: 1622-9; 2014
18. Fervaha G, Agid O, Takeuchi H, Lee J, Foussias G, Zakzanis KK, Graff-Guerrero A, Remington G. Extrapyramidal symptoms and cognitive test performance in patients with schizophrenia. *Schizophrenia Research*. 161: 351-6; 2015
19. Fervaha G, Agid O, Takeuchi H, Foussias G, Lee J, Remington G. Clinical and functional outcomes in people with schizophrenia with a high sense of well-being. *Journal of Nervous and Mental Disease*. 203: 187-93; 2015
20. Fervaha G, Takeuchi H, Lee J, Foussias G, Fletcher PJ, Agid O, Remington G. Antipsychotics and amotivation. *Neuropsychopharmacology*. 40: 1539-48; 2015
21. Nakajima S, Takeuchi H, Fervaha G, Plitman E, Chung JK, Caravaggio F, Iwata Y, Mihashi Y, Gerretsen P, Remington G, Graff-Guerrero A. Comparative efficacy between clozapine and other atypical antipsychotics on depressive symptoms in patients with schizophrenia: Analysis of the CATIE phase 2E data. *Schizophrenia Research*. 161; 429-33: 2015
22. Ohtani A, Suzuki T, Takeuchi H, Uchida H. Language barrier and access to psychiatric care: a systematic review. *Psychiatric Services*. 66: 798-805; 2015
23. *Takeuchi H, Fervaha G, Lee J, Agid O, Remington G. Effectiveness of different dosing regimens of risperidone and olanzapine in schizophrenia. *European Neuropsychopharmacology*. 25: 295-302; 2015
24. Fervaha G, Agid O, Takeuchi H, Lee J, Foussias G, Remington G. Relationship between symptomatic improvement and overall illness severity in patients with schizophrenia. *Journal of Clinical Psychopharmacology*. 35: 128-33; 2015
25. Nakajima S, Takeuchi H, Plitman E, Fervaha G, Gerretsen P, Chung J, Caravaggio F, Iwata Y, Remington G, Graff-Guerrero A. Neuroimaging findings in treatment resistant schizophrenia: A systematic review. *Schizophrenia Research*. 164: 164-75; 2015
26. Lee J, Takeuchi H, Fervaha G, Sin GL, Foussias G, Agid O, Farooq S, Remington G. Subtyping schizophrenia by treatment response: Antipsychotic development and the central role of positive symptoms. *Canadian Journal of Psychiatry*. 60: 515-22; 2015
27. Suzuki T, Uchida H, Sakurai H, Ishizuki T, Tsunoda K, Takeuchi H, Mimura M. Relationships between Global Assessment of Functioning and other rating scales in clinical trials for schizophrenia. *Psychiatry Research*. 30; 227: 265-9; 2015

28. Lee J, Fervaha G, Takeuchi H, Powell V, Remington G. Positive symptoms are associated with clinicians' global impression in treatment-resistant schizophrenia. *Journal of Clinical Psychopharmacology*. 35: 237-41; 2015
29. Suzuki T, Uchida H, Takeuchi H, Tsunoda K, Ishizuki T, Mimura M. Optimization of psychopharmacotherapy for schizophrenia in a male, locked, non-acute unit serving for persistently ill patients over one year. *Psychiatry Research*. 30; 228: 26-30; 2015
30. Ikai S, Suzuki T, Uchida H, Saito H, Mimura M, Takeuchi H. A questionnaire survey of Japanese non-psychiatrists' attitudes on management of depression in a general hospital. *Asian Journal of Psychiatry*. 15: 73-4; 2015
31. Fervaha G, Hill C, Agid O, Takeuchi H, Foussias G, Siddiqui I, Kern RS, Remington G. Examination of the validity of the brief neurocognitive assessment (BNA) for schizophrenia. *Schizophrenia Research*. 166: 304-9; 2015
32. Lee J, Bies R, Takeuchi H, Fervaha G, Bhaloo A, Powell V, Remington G. Quantifying intraindividual variations in plasma clozapine levels: A population pharmacokinetic approach. *Journal of Clinical Psychiatry*. 77:681-7; 2016
33. Lee J, Takeuchi H, Fervaha G, Powell V, Bhaloo A, Bies R, Remington G. The effect of clozapine on hematological indices: A 1-year follow-up study. *Journal of Clinical Psychopharmacology*. 35: 510-6; 2015
34. Ikai S, Suzuki T, Uchida H, Saito H, Mimura M, Takeuchi H. Prescription patterns for depression among consultation-liaison psychiatrists and non-psychiatrists: A chart-review. *International Journal of Geriatric Psychiatry*. 31: 1084-5; 2016
35. Fervaha G, Agid O, Foussias G, Siddiqui I, Takeuchi H, Remington G. Neurocognitive impairment in the deficit subtype of schizophrenia. *European Archives of Psychiatry and Clinical Neuroscience*. 266: 397-407; 2016
36. Chung JK, Plitman E, Nakajima S, Caravaggio F, Takeuchi H, Gerretsen P, Iwata Y, Patel R, Chakravarty M, Mulsant B and Graff-Guerrero A. Depressive symptoms and small hippocampal volume accelerate the progression to dementia from mild cognitive impairment. *Journal of Alzheimer's Disease*. 49: 743-54; 2015
37. *Takeuchi H, Fervaha G, Remington G. Effect of antipsychotic dosing regimen on neurocognition in schizophrenia. *Journal of Clinical Psychopharmacology*. 35: 728-30; 2015
38. Fervaha G, Foussias G, Takeuchi H, Agid O, Remington G. Measuring motivation in people with schizophrenia. *Schizophrenia Research*. 169: 423-6; 2015
39. Tsuboi T, Bies RR, Suzuki T, Takeuchi H, Nakajima S, Graff-Guerrero A, Mamo DC, Caravaggio F, Plitman E, Mimura M, Pollock BG, Uchida H. Predicting plasma olanzapine concentration following a change in dosage: A population pharmacokinetic study. *Pharmacopsychiatry*. 48: 286-91; 2015
40. Fervaha G, Foussias G, Takeuchi H, Agid O, Remington G. Motivational deficits in major depressive disorder: Cross-sectional and longitudinal relationships with functional impairment and subjective well-being. *Comprehensive Psychiatry*. 66: 31-8; 2016
41. *Takeuchi H, Fervaha G, Remington G. Consistency between clinician and patient ratings of clozapine-induced side effects. *Schizophrenia Research*. 174: 200-1; 2016

42. Takeuchi H, Lee J, Fervaha G, Foussias G, Agid O, Remington G. Switching to clozapine using immediate vs. gradual antipsychotic discontinuation: A pilot, double-blind, randomized controlled trial. *Journal of Clinical Psychiatry*. 78: 223-8; 2017
43. *Takeuchi H, Powell V, Geisler S, DeSanti M, Fervaha G, Agid O, Kane JM, Remington G. Clozapine administration in clinical practice: once-daily versus divided dosing. *Acta Psychiatrica Scandinavica*. 134: 234–40; 2016
44. Remington G, Lee J, Agid O, Takeuchi H, Foussias G, Hahn M, Fervaha G, Burton L, Powell V. Clozapine’s critical role in treatment resistant schizophrenia: Ensuring both safety and use. *Expert Opinion on Drug Safety*. 15: 1193-203; 2016
45. *Takeuchi H, Fervaha G, Lee J, Remington G. What symptom domains are associated with patient distress in schizophrenia? *Schizophrenia Research*. 176: 329-30; 2016
46. Fervaha G, Takeuchi H, Foussias G, Agid O, Remington G. Using poverty of speech as a case study to explore the overlap between negative symptoms and cognitive dysfunction. *Schizophrenia Research*. 176: 411-6; 2016
47. Fervaha G, Agid O, Takeuchi H, Foussias G, Remington G. Life satisfaction and happiness among young adults with schizophrenia. *Psychiatry Research*. 242: 174-9; 2016
48. *Takeuchi H, Fervaha G, Lee J, Agid O, Remington G. A preliminary examination of the validity and reliability of a new brief rating scale for symptom domains of psychosis: Brief Evaluation of Psychosis Symptom Domains (BE-PSD). *Journal of Psychiatric Research*. 80: 87-92; 2016
49. *Takeuchi H, Fervaha G, Remington G. Reliability of a patient-reported outcome measure in schizophrenia: results from back-to-back self-ratings. *Psychiatry Research*. 244: 415–9; 2016
50. *Takeuchi H, Fervaha G, Remington G. Incidence of antipsychotic-associated side effects: impact of clinician vs. patient ratings and absolute vs. change scores. *Journal of Clinical Psychopharmacology*. 36: 593-6; 2016
51. Fervaha G, Takeuchi H, Foussias G, Hahn MK, Agid O, Remington G. Achievement motivation in early schizophrenia: relationship with symptoms, cognition and functional outcome. *Early Intervention in Psychiatry*. In press
52. *Takeuchi H, Kantor N, Uchida H, Suzuki T, Remington G. Immediate versus gradual discontinuation in antipsychotic switching: A systematic review and meta-analysis. *Schizophrenia Bulletin*. 43: 862-71; 2017
53. *Takeuchi H, Thiyanavadi S, Fervaha G, Remington G. Neurocognitive benefits of second-generation antipsychotics vs. placebo: Insufficient evidence based on a systematic review. *Journal of Clinical Psychopharmacology*. 37: 274-6; 2017
54. Plitman E, Iwata Y, Caravaggio F, Nakajima S, Chung JK, Gerretsen P, Kim J, Takeuchi H, Chakravarty MM, Remington G, Graff-Guerrero A. Kynurenic acid in schizophrenia: A systematic review and meta-analysis. *Schizophrenia Bulletin*. 43: 764-77; 2017
55. Kirino S, Suzuki T, Takeuchi H, Mimura M, Uchida H. Representativeness of clinical PET study participants with schizophrenia: A systematic review. *Journal Psychiatric Research*. 88: 72-9; 2017
56. Harber L, *Takeuchi H, Borlido C, Hamidian R, Remington G. Factors associated with drug attitude in patients with schizophrenia spectrum disorders. *Schizophrenia Research*. 188: 185-6; 2017
57. Gerretsen P, Takeuchi H, Ozzoude M, Graff-Guerrero A, Uchida H. Insight into illness and its relationship to

illness severity, cognition and estimated antipsychotic dopamine receptor occupancy in schizophrenia: An antipsychotic dose reduction study. *Psychiatry Research*. 251: 20-5; 2017

58. *Takeuchi H, Thiyanavadivel S, Agid O, Remington G. Gradual vs. wait-and-gradual discontinuation in antipsychotic switching: A meta-analysis. *Schizophrenia Research*. In press
59. *Takeuchi H, Kantor N, Sanches M, Fervaha G, Agid O, Remington G. One-year symptom trajectories in patients with stable schizophrenia maintained on antipsychotics vs. placebo: A meta-analysis. *British Journal of Psychiatry*. 211: 137-43; 2017
60. Chung JK, Plitman E, Nakajima S, Caravaggio F, Iwata Y, Gerretsen P, Kim J, Takeuchi H, Shinagawa S, Patel R, Chakravarty MM, Graff-Guerrero A, Alzheimer's Disease Neuroimaging Initiative. Hippocampal and clinical trajectories of mild cognitive impairment with suspected non-Alzheimer's disease pathology. *Journal of Alzheimer's Disease*. 60: 341-7; 2017
61. *Takeuchi H, Thiyanavadivel S, Agid O, Remington G. Rapid vs. slow antipsychotic initiation in schizophrenia: A systematic review and meta-analysis. *Schizophrenia Research*. In press
62. *Takeuchi H, Fathi A, Thiyanavadivel S, Agid O, Remington G. Can aripiprazole worsen psychosis in schizophrenia? A meta-analysis of double-blind, randomized, controlled trials. *Journal of Clinical Psychiatry*. In press

<査読なし英文学術誌>

1. Remington G, Foussias G, Agid O, Hahn M, Takeuchi H, Rao N. Anti-Schizophrenia Drugs: The Next Generation. *Journal of Pakistan Psychiatric Society*. 9: 49-52; 2012
2. *Takeuchi H, Suzuki T, Remington G, Uchida H. Antipsychotic polypharmacy and corrected QT interval: a systematic review. *Canadian Journal of Psychiatry*. 60: 215-22; 2015
3. Remington G, Agid O, Foussias G, Fervaha G, Takeuchi H, Lee J, Hahn M. What Does Schizophrenia Teach Us About Antipsychotics? *Can J Psychiatry*. 60 (3 supplement 2): S14-8; 2015
4. *Takeuchi H, Remington G. Improving symptoms and side effects in older patients with schizophrenia with decreasing dopamine D2/3 receptor occupancy following risperidone and olanzapine dose reduction. *Evidence-Based Mental Health*. 18: 117; 2015
5. Remington G, Foussias G, Fervaha G, Agid O, Takeuchi H, Lee J, Hahn M. Treating Negative Symptoms in Schizophrenia: An update. *Current Treatment Options in Psychiatry*. 3:133-50; 2016

【受賞】

<研究賞>

1. 統合失調症研究会 最優秀賞 (平成 25 年)
2. 日本精神神経学会 精神医学奨励賞 (平成 26 年)
3. University of Toronto, Department of Psychiatry, Best Accomplishment by a Fellow (2014)
4. 日本臨床精神神経薬理学会 ポール・ヤンセン賞 (平成 26 年)
5. 日本精神神経学会 国際学会発表賞 個人発表部門 (平成 27 年)

<トラベルアワード・若手研究者賞>

1. American Society of Clinical Psychopharmacology (ASCP), Workshop on Clinical Trials in

Psychopharmacology Fellowship (2013)

2. University of Toronto, Department of Psychiatry, Fellowship Travel Award (2014)
 3. American Psychiatric Association (APA) Research Colloquium for Junior Investigators (2015)
 4. American Society of Clinical Psychopharmacology (ASCP) Annual Meeting New Investigator Award (2015)
 5. University of Toronto, Department of Psychiatry, Robin Hunter Memorial Award (2015)
 6. The International Society for CNS Clinical Trials and Methodology (ISCTM) New Investigator Award (2016)
- <留学助成・フェローシップアワード>
1. Centre for Addiction and Mental Health (CAMH) Postdoctoral Fellowship Award (2013-2014)
 2. Canadian Institutes of Health Research (CIHR) Fellowship (2014-2017)
 3. Healthy Minds Canada (HMC) Prize in Children's Mental Health (2014)

以上、研修完了報告をさせていただきます。

最後になりましたが、日本臨床精神神経薬理学会の海外研修員として留学する機会を与えていただいたことを心より感謝いたします。5年間充実した留学生活を送ることができたのは、ひとえに日本臨床精神神経薬理学会のご支援のおかげです。今後は海外研修員として学んだことを還元し、我が国の臨床精神薬理分野の発展に貢献できるよう精進する所存です。今後とも変わらぬご指導ご鞭撻のほど、なにとぞよろしくお願い申し上げます。