様　式　Ｃ－１９、Ｆ－１９、Ｚ－１９　（共通）

科学研究費助成事業　　研究成果報告書

平成　２７　年　　６　月　　１　日現在

機関番号：　３３９１６
研究種目：　若手研究(B)
研究期間：　2013～2014
課題番号：　２５８６１０３３

研究課題名（和文）大うつ病性障害におけるエスシタロプラムとパロキセチン徐放製剤のランダム化比較試験

研究課題名（英文）fficacy and tolerability of escitalopram versus paroxetine-CR in Japanese patients with major depressive disorder: a randomized, masked-rater trial

研究代表者
岸　太郎（KISHI, Taro）

藤田保健衛生大学・医学部・講師

研究者番号：４０５３６８０１

交付決定額（研究期間全体）：（直接経費）　　3,200,000円

研究成果の概要（和文）：研究期間内に約100例の患者をエントリーすることができた。本研究は１部の患者は現在も研究が終了していないため、研究報告提出期限内にすべての患者を包括した解析を行うことができなかった。これまで研究が終了している患者のみでの解析では、効果や安全性に関して両群間で統計学的な有意差は認めなかった。今後全患者を対象とした解析で、結果が変わる可能性があることに注意していただきたい。

研究成果の概要（英文）：We included about one hundred patients with major depressive disorder. Some patients who enter the study have not complete the study. Regarding the interim analysis (not all patients include), there were not significant differences in the outcomes with respect to efficacy and safety between both treatment groups.

研究分野：　精神科

キーワード：　大うつ病性障害　エスシタロプラム　パロキセチン徐放製剤

１．研究開始当初の背景

大うつ病性障害は、再発を繰り返す疾患であり、十分な寛解、回復を得るためには長期にわたる治療が必要である。一方で、大うつ病性障害治療においては、抗うつ薬治療開始 1 ヶ月後で約 50%が脱落するという調査結果もあり、抗うつ薬の治療継続性を高めることは大うつ病性障害治療の重要な課題である。昨年国内において上市されたエスシタロプラムは、Meta-Analyses of New Generation Antidepressants (MANGA) MANGA study(Cipriani et al., 2009) をはじめ種々のメタ解析の結果から、良好な治療継続性が期待できる薬剤である(Cipriani et al., 2009)。しかしながら、日本人大うつ病性障害と対象としたエスシタロプラムの臨床試験は報告されていない。更には、日本人大うつ病性障害を対象とした、抗うつ薬同士の直接比較試験も報告がない。また、2012 年 6 月に上市されたパロキセチン徐放製剤は製剤的な工夫から、投与初期に問題となる消化器症状の軽減が期待でき，さらに，反復投与時の薬物血中濃度の変動が小さくなることで全般的忍容性の向上とともに治療継続に寄与できる，と報告されている。尚、パロキセチン徐放製剤と他の抗うつ薬を比較した RCT は、世界的にも、現在まで報告がなかった。

２．研究の目的

これまでの大うつ病性障害における RCT の outcome は、効果、忍容性に焦点を当てた研究が大半を占める。しかしながら、実臨床において、「症状の重症度評価スケールでは点数は極めて改善しているのに、復職できない」といった患者が散見される。そのため、本研究の特徴でもあるが、PSP（Personal and Social Performance Scale）を用いて社会機能回復度の評価も行う。更に、重症度と社会機能回復度の得点が関連しない場合、今後の大うつ病性障害の臨床研究において、従来の重症度評価のみならず社会機能回復度評価の必要であるということ証明できるかもしれない。以上から、本研究は、世界初の日本人大うつ病性障害患者に対し、エスシタロプラムとパロキセチン徐放製剤のランダム化比較試験を行い、有効性および安全性について検討し、日本人大うつ病性障害患者における抗うつ薬のエビデンスを構築することを目的とした。

３．研究の方法

対象患者:DSM-Ⅳ-TR による主診断が大うつ病性障害と診断された外来通院及び入院中の患者(SCID-1を用いて診断)でHAM-D17の合計点が 20 点以上の患者

調査方法：コンピューターにて治療薬を無作為割付け（中央登録方式），評価者盲検化本研究（24 週）は、0 週、1 週、2 週、4 週、8 週、12 週、24 週および脱落時に評価を行う。

(1) 効果：ハミルトンのうつ病尺度得点の推移、治療反応率、寛解率
(2) 安全性（Udvalg for kliniske undersogelser 副作用スケール）：薬剤間での違いの解明
(3) 忍容性：それぞれの薬剤の治療中断率の比較
(4) 社会機能回復度（Personal and Social Performance Scale）

４．研究成果

研究期間内に約 100 例の患者をエントリーすることができた。本研究は１部の患者は現在も研究が終了していないため、研究報告提出期限内にすべての患者を包括した解析を行うことができなかった。これまで研究が終了している患者のみでの解析では、効果や安全性に関して両群間で統計学的な有意差は認めなかった。今後全患者を対象とした解析で、結果が変わる可能性があることに注意していただきたい。

５．主な発表論文等

（研究代表者、研究分担者及び連携研究者には下線）

〔雑誌論文〕（計　54 件）

1. **Kishi T,** Matsuda Y, Matsunaga S, Iwata N. Aripiprazole for the management of schizophrenia in the Japanese population: a systematic review and meta-analysis of randomized controlled trials. Neuropsychiatr Dis Treat. 2015 Feb 20;11:419-34. doi: 10.2147/NDT.S78977. eCollection 2015.

2. Matsunaga S, **Kishi T,** Iwata N. Memantine for Alzheimer's disease: A Systematic Review and Meta-analysis. PLOS ONE. 2015 in press

3. **Kishi T,** Matsuda Y, Mukai T, Matsunaga S, Yasue I, Fujita K, Okochi T, Hirano S, Kajio Y, Funahashi T, Akamatsu K, Ino K, Okuda M, Tabuse H, Iwata N. A cross-sectional survey to investigate the prevalence of pain in Japanese patients with major depressive disorder and schizophrenia. Compr Psychiatry. 2015 in press.

4. Matsunaga S, **Kishi T,** Iwata N. Combination Therapy with Cholinesterase Inhibitors and Memantine for Alzheimer's disease: A Systematic Review and Meta-analysis. Int J Neuropsychopharmacol. 2014 in press

5. **Kishi T,** Matsunaga S, Matsuda Y, Iwata N. Iminodibenzyl class antipsychotics for schizophrenia: a systematic review and meta-analysis of carpipramine, clocapramine and mosapramine.

Neuropsychiatric Disease and Treatment 2014 in press

6. **Kishi T,** Iwata N. Varenicline for smoking cessation in people with schizophrenia: systematic review and meta-analysis. Eur Arch Psychiatry Clin Neurosci. 2014 in press

7. **Kishi T**, Matsuda Y, Fujita K, Iwata N. Early prediction of blonanserin response in Japanese patients with schizophrenia. Neuropsychiatric Disease and Treatment. 2014 in press

8. **Kishi T**, Iwata N. Efficacy and Tolerability of Histamine-2 Receptor Antagonist Adjunction of Antipsychotic Treatment in Schizophrenia: A Meta-Analysis of Randomized Placebo-Controlled Trials / Histamine-2 Receptor Antagonists for Schizophrenia. Pharmacopsychiatry. 2014 in press

9. **Kishi T**, Matsuda Y, Iwata N. The Position of Blonanserin as a Treatment for Schizophrenia. Asia- Pacific Psychiatry. 2014 in press

10. Matsuda A, Miyashita M, Matsumoto S, Matsutani T, Sakurazawa N, Takahashi G, Kishi T, Uchida E. Comparison of Long-Term Outcomes of Colonic Stent as "Bridge to Surgery" and Emergency Surgery for Malignant Large-Bowel Obstruction: A Meta-Analysis. Ann Surg Oncol. 2014 in press

11. Matsuda A, Miyashita M, Matsumoto S, Takahashi G, Matsutani T, Yamada T, **Kishi T**, Uchida E. Abdominoperineal Resection Provides Better Local Control But Equivalent Overall Survival to Local Excision of Anorectal Malignant Melanoma: A Systematic Review. Ann Surg. 2014 in press

12. Oya K, **Kishi T**, Iwata N. Efficacy and tolerability of minocycline augmentation therapy in schizophrenia: a systematic review and meta-analysis of randomized controlled trials. Hum Psychopharmacol. 2014 in press

13. Hayashi K, Yoshimura R, Kakeda S, **Kishi T**, Abe O, Umene-Nakano W, Katsuki A, Hori H, Ikenouchi-Sugita A, Watanabe K, Ide S, Ueda I, Moriya J, Iwata N, Korogi Y, Kubicki M, Nakamura J. COMT Val158Met, but not BDNF Val66Met, is associated with white matter abnormalities of the temporal lobe in patients with first-episode, treatment-naïve major depressive disorder: a diffusion tensor imaging study. Neuropsychiatr Dis Treat. 2014 Jun 25;10:1183-90.

14. **Kishi T**, Matsuda Y, Iwata N. Cardiometabolic Risks of Blonanserin and Perospirone in the Management of Schizophrenia: A Systematic Review and Meta-analysis of Randomized Controlled Trials. PLoS ONE. 2014. in press

15. Yoshimura R, **Kishi T**, Hori H, Katsuki A, Sugita-Ikenouchi A, Umene-Nakano W, Atake K, Iwata N, Nakamura J. Serum Levels of Brain-Derived Neurotrophic Factor at 4 Weeks and Response to Treatment with SSRIs. Psychiatry Investig. 2014 Jan;11(1):84-8.

16. **Kishi T**, Hori H, Fukuoa Y, Moriwakia M, Yoshimura R, Katsuki A, Ikenouchi-Sugita A, Atake K, Umene-Nakano W, Kaneda Y, Fujita K, Nakamura J, Iwata N. No significant association between brain-derived neurotrophic factor gene rs6265 and cognitive function in Japanese patients with schizophrenia. Psychiatry Research. 2014. in press

17. Matsunaga S, **Kishi T**, Iwata N. Memantine for Lewy body disorders: Systematic Review and Meta-analysis. Am J Geriatr Psychiatry. 2013. in press

18. **Kishi T**, Meltzer HY, Matsuda Y, Iwata N. Azapirone 5-HT1A Receptor Partial Agonist Treatment for Major Depressive Disorder: Meta-analysis and Systematic Review. Psychological Medicine. 2013. in press

19. Mukai T, **Kishi T**, Matsuda Y, Iwata N. A meta-analysis of inositol for depression and anxiety disorders. Hum Psychopharmacol. 2013. in press

20. Hirota T. Veenstra-Vanderweele J, Hollander E, **Kishi T**, Antiepileptic medications in autism spectrum disorder: a systematic review and meta-analysis. J Autism Dev Disord.

2013. In press

21. Matsuda Y, **Kishi T**, Iwata N, Efficacy and Safety of NMDA Receptor Antagonists Augmentation Therapy for Schizophrenia: An Updated Meta-analysis of Randomized Placebo-controlled Trials. J Psychiatr Res. 2013. in press

22. Zhao Y, Kishi T, Iwata N, Ikeda M, Combination Treatment with Risperidone Long Acting Injection and Psycho-educational Approaches for Preventing Relapse in Schizophrenia. Neuropsychiatr Dis Treat. 2013. in press

23. **Kishi T**, Matsuda Y, Correll CU, Iwata N, Antipsychotics for Cocaine or Psychostimulant Dependence: Systematic Review and Meta-analysis of Randomized, Placebo-Controlled Trials. J Clin Psychiatry. 2013. in press

24. Hirota T. **Kishi T**, Prophylactic Antipsychotic Use for Postoperative Delirium: A Systematic Review and Meta-Analysis. J Clin Psychiatry. 2013. in press

25. **Kishi T**, Mukai T, Matsuda Y, Iwata N. Selective Serotonin 3 Receptor Antagonist Treatment for Schizophrenia: Meta-analysis and Systematic Review. Neuromolecular Med. 2013. in press

26. **Kishi T**, Mukai T, Matsuda Y, Moriwaki M, Iwata N. Efficacy and Safety of Noradrenalin Reuptake Inhibitor Augmentation Therapy for Schizophrenia: A Meta-Analysis of Double-blind Randomized Placebo-Controlled Trials. J Psychiatr Res. 2013. in press

27. **Kishi T**, Iwata N. Efficacy and Tolerability of Perospirone in Schizophrenia: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. CNS Drugs. 2013. in press

28. Hirota T. **Kishi T**, Adenosine Hypothesis in Schizophrenia and Bipolar Disorder: A Systematic Review and Meta-Analysis of Randomized Controlled Trial of Adjuvant Purinergic Modulators. Schizophrenia Research. 2013. in press

29. **Kishi T**, Iwata N. Meta-Analysis of Noradrenergic and Specific Serotonergic Antidepressant Use In Schizophrenia. The International Journal of Neuropsychopharmacology. 2013. in press

30. **Kishi T**, Meltzer HY, Iwata N. Augmentation of antipsychotic drug action by azapirone serotonin$_{1A}$ receptor partial agonists: A Meta-Analysis. The International Journal of Neuropsychopharmacology. 2013. in press

31. Matsuda A, Miyashita M, Matsumoto S, Matsutani T, Sakurazawa N, Akagi I, **Kishi T**, Yokoi K, Uchida E. Hepatic Pedicle Clamping Does Not Worsen Survival after Hepatic Resection for Colorectal Liver Metastasis: Results from a Systematic Review and Meta-analysis. Ann Surg Oncol. 2013. in press

32. Nagao K, **Kishi T**, Moriwaki M, Fujita K, Hirano S, Yamanouchi Y, Funahashi T, Iwata N. Comparative clinical profile of mirtazapine and duloxetine in practical clinical settings in Japan: a 4-week open-label, parallel-group study of major depressive disorder. Neuropsychiatr Dis Treat. 2013;9:781-6.

33. Esaki K, Kondo K, Hatano M, Saito T, **Kishi T**, Umene-Nakano W, Yoshimura R, Nakamura J, Ozaki N, Ikeda M, Iwata N. Further evidence of an association between a genetic variant in BMP7 and treatment response to SSRIs in major depressive disorder. J Hum Genet. 2013. in press

34. **Kishi T**, Hirota T, Iwata N. Add-on fluvoxamine treatment for schizophrenia: an updated meta-analysis of randomized controlled trials. Eur Arch Psychiatry Clin Neurosci. 2013. in press

35. **Kishi T**, Iwata N. NMDA receptor antagonists interventions in schizophrenia: Meta-analysis of randomized, placebo-controlled trials. J Psychiatr Res. 2013. in press

36. **Kishi T**, Fukuo Y. Okochi T. Kawashima

K. Moriwaki M. Furukawa O. Musso GM. Fujita K. Correll CU. Iwata N. Relationship between Nicotine Dependence and the Endophenotype-related Trait of Cognitive Function but not Acoustic Startle Reponses in Japanese Patients with Schizophrenia. Hum Psychopharmacol. 2013. in press

37. **Kishi T,** Sevy S, Chekuri R, Correll CU. Antipsychotics are Ineffective for Primary Alcohol Dependence: Results from a Systematic Review and Meta-analysis of Placebo-Controlled Trials. Results from a systematic review and meta-analysis. J Clin Psychiatry. 2013. in press

38. Matsuda Y, **Kishi T**, Nakamura H, Iwata N, Yokukansan in the Treatment of Behavioral and Psychological Symptoms of Dementia: A Systematic Review and Meta-analysis of Randomized Controlled Trials. Hum Psychopharmacol. 2013. in press

39. **Kishi T**, Fujita F, Furukawa O, Suzuki T, Moriwaki M, Nitta M, Hattori M, Tsunoka T, Chekuri R, Kane JM, Correll CU, Iwata N. Efficacy and Tolerability of Clozapine in Japanese Patients with Treatment-Resistant Schizophrenia: Results from a 12-Week, Flexible Dose Study Using Raters Masked to Antipsychotic Choice. Asian J Psychiatr. 2013 Jun;6(3):200-7

40. **Kishi T**, Suzuki T, Sekiguchi H, Moriwaki M, Okuda A, Mekata T, Hattori M, Tsunoka T, Chekuri R, Musso GM, Fujita K, Iwata N. Efficacy and Tolerability of High Dose Olanzapine in Japanese Patients with Treatment-Resistant Schizophrenia. 2013 Feb;6(1):86-7

41. Matsuda A, **Kishi T**, Musso G, Matsutani T, Yokoi K, Wang P, Uchida E. The Effect of Intraoperative Rectal Washout on Local Recurrence after Rectal Cancer Surgery: A Meta-Analysis. Ann Surg Oncol. 2013 Mar;20(3):856-63

42. **Kishi T**, Yoshimura R, Fukuo Y, Okochi T, Matsunaga S, Umene-Nakano W, Nakamura J, Serretti A, Correll CU, Kane JM, Iwata N. The serotonin 1A receptor gene confer susceptibility to mood disorders: results from an extended meta-analysis of patients with major depression and bipolar disorder. Eur Arch Psychiatry Clin Neurosci. 2013 Mar;263(2):105-18

43. Kishimoto T, Agarwal V, **Kishi T**, Leucht S, Kane JM, Correll CU. Relapse prevention in schizophrenia: a systematic review and meta-analysis of second-generation antipsychotics versus first-generation antipsychotics. Mol Psychiatry. 2013 Jan;18(1):53-66

44. Matsuda A, Matsumoto S, Seya T, Mamada Y, Matsutani T, Tsuruta H, Sasaki J, Sakurazawa, **Kishi T**, Yokoi K, Ping W, Uchida E, Does Postoperative Complication Have a Negative Impact on Long-Term Outcomes following Hepatic Resection for Colorectal Liver Metastasis? : A Meta-Analysis. Ann Surg Oncol. 2013 Aug;20(8):2485-92

45. **Kishi T**, Matsuda Y, Nakamura H, Iwata N, Blonanserin for schizophrenia: Systematic review and meta-analysis of double-blind, randomized, controlled trials. J Psychiatr Res. 2013 Feb;47(2):149-54. doi: 10.1016/j.jpsychires.2012.10.011. Epub 2012 Nov 3.

46. Yoshimura R, **Kishi T**, Hori H, Ikenouchi-Sugita A, Umene-Nakano W, Katsuki A, Hayashi K, Iwata N, Nakamura J. No Association between the Response to the Addition of an Atypical Antipsychotic Drug to an SSRI or SNRI and the BDNF (Val66Met) Polymorphism in Refractory Major Depressive Disorder in Japanese Patients. Clin Psychopharmacol Neurosci. 2012 Apr;10(1):49-53. doi: 10.9758/cpn.2012.10.1.49.

47. **Kishi T**, Kafantaris V, Sunday S, Sheridan EM, Correll CU. Are antipsychotics effective for the treatment of anorexia nervosa? Results from a systematic review and meta-analysis. J Clin Psychiatry. 2012 Jun;73(6):e757-66. Review.

48. Matsunaga S, Ikeda M, **Kishi T**, Fukuo Y, Aleksic B, Yoshimura R, Okochi T, Yamanouchi Y, Kinoshita Y, Kawashima K, Umene-Nakano W, Inada T, Kunugi H, Kato T, Yoshikawa T, Ujike H, Nakamura J,

Ozaki N, Kitajima T, Iwata N. An evaluation of polymorphisms in casein kinase 1 delta and epsilon genes in major psychiatric disorders. Neurosci Lett. 2012 Sep 7. pii: S0304-3940(12)01164-0. doi: 10.1016/j.neulet.2012.08.070.

49. Matsuda A, **Kishi T**, Jacob A, Aziz M, Wang P. Association between insertion/deletion polymorphism in angiotensin-converting enzyme gene and acute lung injury/acute respiratory distress syndrome: a meta-analysis. BMC Med Genet. 2012 Aug 31;13(1):76.

50. Katsuki A, Yoshimura R, **Kishi T**, Hori H, Umene-Nakano W, Ikenouchi-Sugita A, Hayashi K, Atake K, Iwata N, Nakamura J. Serum levels of brain-derived neurotrophic factor (BDNF), BDNF gene Val66Met polymorphism, or plasma catecholamine metabolites, and response to mirtazapine in Japanese patients with major depressive disorder (MDD). CNS Spectr. 2012 Sep;17(3):155-63.

51. Yoshimura R, **Kishi T**, Hori H, Ikenouchi-Sugita A, Katsuki A, Umene-Nakano W, Iwata N, Nakamura J. Comparison of the efficacy between paroxetine and sertraline augmented with aripiprazole in patients with refractory major depressive disorder. Prog Neuropsychopharmacol Biol Psychiatry. 2012 Dec 3;39(2):355-7.

52. **Kishi T**, Ichinose H, Yoshimura R, Fukuo Y, Kitajima T, Inada T, Kunugi H, Kato T, Yoshikawa T, Ujike H, Musso GM, Umene-Nakano W, Nakamura J, Ozaki N, Iwata N. GTP cyclohydrolase 1 gene haplotypes as predictors of SSRI response in Japanese patients with major depressive disorder. J Affect Disord. 2012 Dec 15;142(1-3):315-22

53. **Kishi T**, Fukuo Y, Okochi T, Kawashima K, Kitajima T, Inada T, Ozaki N, Musso GM, Kane JM, Correll CU, Iwata N. Serotonin 6 receptor gene and schizophrenia: case-control study and meta-analysis. Hum Psychopharmacol. 2012 Jan;27(1):63-9.

54. **Kishi T**, Fukuo Y, Okochi T, Kawashima K, Moriwaki M, Furukawa O, Fujita K, Musso GM, Correll CU, Kane JM, Iwata N. The relationship between acoustic startle response measures and cognitive functions in Japanese patients with schizophrenia. Neuromolecular Med. 2012 Jun;14(2):131-8.

〔学会発表〕(計 1 件)

Taro Kishi, A Randomized Study of Escitalopram and Paroxetine Controlled-Release in the Treatment of Japanese Major Depressive Disorder, 26th-ECNPCongress, 5-9 October 2013, Barcelona, Spain

６．研究組織

(1)研究代表者

岸 太郎 (Kishi Taro)

藤田保健衛生大学医学部 講師

研究者番号：40536801