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# 学位論文内容の要旨


**Purpose:**

Benzodiazepines (BZDs) are prescribed to treat psychiatric diseases. However, many guidelines recommend limiting the use of BZDs because of side effects and lack of evidence regarding long-term efficacy. Moreover, reducing BZDs' use is difficult because of dependency and the severity of withdrawal symptoms. The efficacy of cognitive behavioral therapy (CBT) for mood and anxiety disorders has been demonstrated. However, there is scant evidence that CBT has effectively reduced BZDs use, especially in Japan, where the BZDs prescription rate is high. Therefore, we sought to examine the impact of CBT on reducing BZDs use in a Japanese psychiatric setting.

**Patients and Methods:**

Participants were outpatients with mood and anxiety disorders who were prescribed BZD anxiolytics. We retrospectively reviewed changes in BZD anxiolytics prescription dosages during CBT (66 patients; mean number of CBT sessions, 14.6) from our hospital record between April 2015 and September 2017. We checked prescriptions at four time points: at first interview for judging adaptation of CBT (baseline), at the first CBT session, at the last CBT session, and 3 months after the last CBT session. To estimate the effect of CBT on discontinuation or dose-reduction, we compared the prescription-dose at baseline with that after CBT or at follow-up (3 months post-CBT) using a Bayesian hierarchical hurdle regression model. The prescription-dose distribution was expected to be a skewed, non-normal distribution, with values generally concentrated at zero or low dose. Estimates of the gamma and log-normal mixed regression model were compared using information criteria, such as the widely applicable information criterion (WAIC). To compare the baseline and each time point (post-CBT or follow-up), the time point was input into the model as a categorical variable, and estimation was performed using a hierarchical model in which the participants' IDs were set as random effects. We assumed a different mechanism for discontinuation or dose reduction; generally, discontinuation

occurs based on the careful clinical judgment after a certain low-dose period, rather than a gradual linear reduction as a function of time. Dose reduction is expected to decrease gradually. Thus, we assumed a model that simultaneously estimates a binary outcome logistic model, such as whether a threshold is exceeded, as well as a model that explains the linear relationship between outcomes and explanatory variables for samples that exceed the threshold (hurdle). Furthermore, we estimated whether the prescription-dose was zero or not as a withdrawal effect and a change in the prescription amount as a reduction effect. Bayesian hierarchical hurdle regression models were estimated for the prescription dose of BZD anxiolytics, antidepressants, and hypnotics. We included sex and age into the model as covariates.

**Results:**

A total of 13 of 66 patients discontinued BZD anxiolytics during CBT, and 21 of 66 reduced their prescribed dosage by 50%. The association between discontinuation and dose-reduction and assessment period was modeled simultaneously using Bayesian hierarchical hurdle model. Results from the modeling showed a significant discontinuation at post-CBT and at 3 months post-CBT session compared to baseline (estimated median odds ratio [OR] post-CBT = 9.79 [95% CI: 4.65- 20.45]; OR at 3 months post-CBT = 11.53 [95% CI: 6.06- 22.33]). Moreover, a significant dose reduction was observed post-intervention (estimated median relative risk = 0.845 [95% CI: 0.729- 0.982]), with a median reduction of 1.7 mg (diazepam conversion) in BZD use.

**Discussion:**

A possible explanation for the finding that participants reduce and discontinue BZD anxiolytics during CBT and that this reducing effect remains after the end of CBT sessions is that they can learn how to manage their anxiety symptoms during treatment. Otto et al (2002) indicated that BZD anxiolytics just suppress anxiety symptoms, and if patients reduce them, they feel anxiety again, especially patients with panic disorder. The authors also suggested that patients may reduce BZD anxiolytics by managing their anxiety symptoms using core skills acquired by CBT, including informational, cognitive, and exposure skills. The CBT used in our study also included these core skills; therefore, we can assume similar effects. This study has some limitations. First, we were unable to quantify the patients' anxiety and to determine the reasons underlying the changes in BZD anxiolytics dose. Second, we did not include a control group. Thus, the precise factors underlying the
reduction and discontinuation of BZD anxiolytics are unclear. Lastly, we gathered data from heterogeneous patients, which has both benefits and limitations. Therefore, we cannot categorically state that a specific CBT effectively reduces the use of BZD anxiolytics or that this is observed for patients with specific diagnoses. Nevertheless, the present results suggest that different patients who are prescribed BZD anxiolytics may be able to reduce or discontinue their medicines following individually tailored CBT. Future studies with a unified parameter and stricter research design are needed to examine the efficacy of CBT in reducing BZD anxiolytics use in Japan. Despite these limitations and taking into account that few studies have examined the relationship between CBT and BZD anxiolytics, we consider that our study has important clinical relevance regarding the role of CBT in reducing BZD anxiolytics use.

**Conclusion:**

Our results suggest that CBT possibly aids in reducing and discontinuing BZD anxiolytics use for Japanese patients.

# 論文審査結果の要旨

本研究は、「不安障害や気分障害の患者に認知行動療法を行うとベンゾジアゼピン系抗不安薬の量は減少するか」というリサーチクエスチョンについて検討した研究である。2015 年 4 月～2017 年 9 月に国立精神・神経センターの認知行動療法専門外来を受診して気分障害または不安障害と診断され、ベンゾジアゼピン系抗不安薬を定時内服し、認知行動療法（週 1 回 40～50 分、全 8～16 回）を受けた患者 66 名を対象としている。方法として、これらの患者の認知行動療法専門外来初診時と、認知行動療法直後と 3 ヶ月後の処方量を比較検討している（後方視的観察研究）。

研究結果では、3 ヶ月後に 13 名（20%）が断薬でき、21 名（32%）が 50%以上減薬できていた。海外での先行研究と同様に、認知行動障害はベンゾジアゼピン系抗不安薬を減薬できていた。一方、断薬については、欧米の先行研究では 56～74%、本研究では 20%と乖離が見られた。この乖離については、先行研究では、断薬を希望する患者をリクルートした前向きの介入研究であったこと、本研究では、比較的罹病期間が長く、高用量（5mg/day）のベンゾジアゼピン系抗不安薬を服用している患者が多かったことが影響したと考えられた。

本研究は、コントロール群を置いた前向き介入研究ではないものの、認知行動療法が不安障害や気分障害の患者のベンゾジアゼピン系抗不安薬の減薬・断薬をもたらす可能性があることを示した、日本ではじめての研究である点が評価できる。この研究結果により、実臨床での認知行動療法が普及して、患者のベンゾジアゼピン系抗不安薬の減薬・断薬に繋がることを期待したい。

申請者は人格、見識、能力ともに優れており、研究成果、研究に対する真摯な態度、今後の研究への意欲など総合的に考えて、本学の博士（医学）の学位を授与するに相応しいと全員一致で判断した。