Research Square

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Predictors of chronic etizolam use among newly treated patients: a 21-year retrospective cohort study

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Abstract

Background

Etizolam, a thienodiazepine anxiolytic widely prescribed in Japan, has raised concerns regarding long-term use and dependence. Although regulatory efforts have aimed to reduce benzodiazepine-related prescribing, little is known about long-term continuation patterns among newly prescribed etizolam users.

Methods

We conducted a retrospective cohort study using prescription data from a Japanese university hospital between April 2001 and March 2022. Newly prescribed etizolam users were identified according to the fiscal year of initial prescription. Continuation rates at 3 months, 6 months, and 1 year were examined. Chronic etizolam use was primarily defined as continuation for ≥ 3 months. Logistic regression analyses were conducted to identify factors associated with chronic use.

Results

A total of 12,771 newly prescribed etizolam users were identified during the study period. The number of newly prescribed patients and continuation rates gradually decreased over time, with significant temporal trends observed at 3 months, 6 months, and 1 year (all $p < 0.001$). Among patients prescribed etizolam between fiscal years 2001 and 2020, 3,981 of 12,519 patients (31.8%) continued treatment for ≥ 3 months. Older age, higher initial dose, longer initial prescription duration, and department type were independently associated with chronic use. No significant sex differences were observed.

Conclusions

Although newly prescribed etizolam users decreased over two decades, chronic use remained common in a substantial proportion of patients. Older age and initial prescribing characteristics may contribute to long-term continuation. Careful prescribing and deprescribing support may help reduce chronic etizolam exposure.

1. Introduction

Etizolam is a thienodiazepine anxiolytic and hypnotic agent that has been widely prescribed in Japan for insomnia, anxiety, and psychosomatic symptoms [1, 2]. Despite increasing concerns regarding dependence, withdrawal symptoms, cognitive impairment, and falls in older adults [2–4], etizolam has continued to be used in routine clinical practice, including non-psychiatric settings. Previous studies have suggested that long-term benzodiazepine receptor agonist use remains common, particularly among older patients and those with chronic insomnia or anxiety symptoms [5, 6].

In response to these concerns, several regulatory and guideline-based interventions have been implemented in Japan. In 2016, the prescription duration of etizolam was, in principle, restricted to a maximum of 30 days [7]. Furthermore, revisions to the national medical fee schedule introduced financial disincentives for prolonged benzodiazepine prescribing. Clinical practice guidelines have also emphasized minimizing long-term benzodiazepine use and promoting safer alternatives [8].

Although previous studies have reported temporal changes in benzodiazepine prescribing patterns, most analyses have focused on prescription-level trends rather than patient-level continuation patterns. Consequently, little is known about how frequently newly prescribed etizolam users continue treatment long term, and which clinical factors are associated with chronic use. Understanding these patient-level continuation patterns is important because long-term benzodiazepine exposure is associated with dependence, adverse events, and difficulties in deprescribing [9, 10].

Etizolam may warrant particular attention because of its distinctive prescribing profile in Japan. Unlike many other hypnotic agents, etizolam has historically been prescribed not only in psychiatric practice but also across various non-psychiatric departments [11, 12]. In addition, its dual use for both anxiolytic and hypnotic purposes may contribute to continued long-term prescribing despite regulatory interventions.

Therefore, the present study aimed to investigate long-term continuation patterns among newly prescribed etizolam users at a Japanese university hospital over a 21-year period. Specifically, we examined temporal trends in continuation rates and identified factors associated with chronic etizolam use using patient-level retrospective cohort data.

2. Methods

2.1. Study setting

This retrospective cohort study was conducted using electronic medical record (EMR)-based prescription data from a tertiary university hospital in Japan between 1 April 2001 and 31 March 2022. The hospital was newly established in April 2001, corresponding to the beginning of the study period. Therefore, all etizolam prescriptions recorded during fiscal year 2001 were regarded as newly initiated prescriptions within this hospital database. All clinical activities, including prescribing, were managed using a hospital-wide computerized EMR system throughout the study period. Complete prescription records were available without missing data. The study was approved by the Ethics Committee of Showa Medical University (approval no. 22-038-A) and was conducted in accordance with institutional guidelines.

2.2. Study population and definitions

Patients who newly received etizolam during the study period were identified using prescription records. Newly prescribed etizolam users were defined as patients who received their first recorded etizolam prescription within the hospital database during the study period. Patients were classified according to the fiscal year of initial etizolam prescription, defined from April to March of the following year in accordance with the Japanese fiscal year system.

Continuation of etizolam treatment was assessed at 3 months, 6 months, 1 year, 2 years, and annually thereafter until the end of the study period. Patients who continued to receive etizolam prescriptions for at least 3 months after treatment initiation were defined as chronic etizolam users. Patients prescribed etizolam for < 3 months were classified as non-chronic users. Sensitivity analyses were additionally performed using alternative definitions of chronic use (≥ 6 months and ≥ 1 year).

2.3. Variables assessed

The following variables were evaluated at the time of the initial etizolam prescription: age, sex, department type, initial prescription dose, and initial prescription duration. Clinical departments were categorized into psychiatry, internal medicine, surgery and others, based on the clinical classification system used in the hospital. Because patients could receive care from multiple departments during follow-up, department type was defined based on the department issuing the initial etizolam prescription.

2.4. Statistical analysis

Temporal trends in continuation rates at 3 months, 6 months, and 1 year were evaluated using the Cochran–Armitage trend test. Univariate and multivariable logistic regression analyses were conducted to identify factors associated with chronic etizolam use. The dependent variable was chronic etizolam use (yes/no). Independent variables included age, sex, department type, initial prescription dose, initial prescription duration, and fiscal year of treatment initiation. Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. Sensitivity analyses using alternative chronic-use definitions (≥ 6 months and ≥ 1 year) were additionally performed. All statistical analyses were performed using SAS software version 9.4 [13]. A two-sided P value < 0.05 was considered statistically significant.

3. Results

3.1. Patient characteristics and continuation rates

A total of 12,771 newly prescribed etizolam users were identified during the study period. The annual number of newly prescribed patients gradually decreased over time (Fig. 1). Continuation rates at 3 months, 6 months, and 1 year also showed significant decreasing temporal trends across fiscal years (all Cochran–Armitage trend tests, $p < 0.001$) (Table 1). However, a substantial proportion of patients continued long-term etizolam treatment throughout the study period. Among patients prescribed etizolam between fiscal years 2001 and 2020, 3,981 of 12,519 patients (31.8%) continued treatment for at least 3 months and were classified as chronic etizolam users.

Table 1
Follow-up results of 12,771 patients prescribed during fiscal years (FY) 2001 to 2021.

FY of initial etizolam prescriptions	Newly prescribed patients	Follow-up									
		3 months	6 months	1 year	2 years	3 years	4 years	5 years	10 years	15 years	20 years
FY2001	887 (100%)	328 (37.0%)	189 (21.3%)	123 (13.9%)	77 (8.7%)	56 (6.3%)	39 (4.4%)	34 (3.8%)	10 (1.1%)	2 (0.2%)	1 (0.1%)
FY2002	1,080 (100%)	416 (38.5%)	252 (23.3%)	164 (15.2%)	109 (10.1%)	75 (6.9%)	61 (5.6%)	53 (4.9%)	16 (1.5%)	4 (0.4%)	-
FY2003	888 (100%)	284 (32.0%)	164 (18.5%)	107 (12.0%)	60 (6.8%)	46 (5.2%)	33 (3.7%)	25 (2.8%)	8 (0.9%)	3 (0.3%)	-
FY2004	847 (100%)	259 (30.6%)	127 (15.0%)	80 (9.4%)	59 (7.0%)	41 (4.8%)	35 (4.1%)	25 (3.0%)	5 (0.6%)	2 (0.2%)	-
FY2005	1,175 (100%)	379 (32.3%)	206 (17.5%)	134 (11.4%)	95 (8.1%)	71 (6.0%)	54 (4.6%)	39 (3.3%)	9 (0.8%)	4 (0.3%)	-
FY2006	1,225 (100%)	373 (30.4%)	223 (18.2%)	140 (11.4%)	86 (7.0%)	64 (5.2%)	45 (3.7%)	38 (3.1%)	13 (1.1%)	4 (0.3%)	-
FY2007	921 (100%)	294 (31.9%)	167 (18.1%)	105 (11.4%)	67 (7.3%)	36 (3.9%)	28 (3.0%)	16 (1.7%)	4 (0.4%)	-	-
FY2008	744 (100%)	238 (32.0%)	131 (17.6%)	84 (11.3%)	37 (5.0%)	25 (3.4%)	20 (2.7%)	16 (2.2%)	4 (0.5%)	-	-
FY2009	671 (100%)	222 (33.1%)	119 (17.7%)	66 (9.8%)	44 (6.6%)	27 (4.0%)	22 (3.3%)	17 (2.5%)	7 (1.0%)	-	-
FY2010	625 (100%)	199 (31.8%)	122 (19.5%)	81 (13.0%)	54 (8.6%)	34 (5.4%)	23 (3.7%)	18 (2.9%)	5 (0.8%)	-	-
FY2011	534 (100%)	190 (35.6%)	107 (20.0%)	64 (12.0%)	41 (7.7%)	30 (5.6%)	19 (3.6%)	18 (3.4%)	5 (0.9%)	-	-
FY2012	447 (100%)	137 (30.6%)	78 (17.4%)	47 (10.5%)	25 (5.6%)	15 (3.4%)	12 (2.7%)	8 (1.8%)	-	-	-
FY2013	411 (100%)	118 (28.7%)	64 (15.6%)	38 (9.2%)	21 (5.1%)	14 (3.4%)	10 (2.4%)	8 (1.9%)	-	-	-
FY2014	374 (100%)	127 (34.0%)	72 (19.3%)	48 (12.8%)	27 (7.2%)	22 (5.9%)	16 (4.3%)	13 (3.5%)	-	-	-
FY2015	317 (100%)	105 (33.1%)	60 (18.9%)	40 (12.6%)	23 (7.3%)	14 (4.4%)	10 (3.2%)	7 (2.2%)	-	-	-
FY2016	358 (100%)	128 (35.8%)	59 (16.5%)	37 (10.3%)	21 (5.9%)	12 (3.4%)	10 (2.8%)	7 (2.0%)	-	-	-
FY2017	293 (100%)	74 (25.3%)	32 (10.9%)	19 (6.5%)	11 (3.8%)	11 (3.8%)	6 (2.0%)	-	-	-	-
FY2018	256 (100%)	71 (27.7%)	43 (16.8%)	24 (9.4%)	15 (5.9%)	12 (4.7%)	-	-	-	-	-
FY2019	200 (100%)	53 (26.5%)	34 (17.0%)	19 (9.5%)	13 (6.5%)	-	-	-	-	-	-
FY2020	266 (100%)	61 (22.9%)	34 (12.8%)	23 (8.6%)	-	-	-	-	-	-	-
FY2021	252 (100%)	[-2.860 (P = 0.004)][a]	[-2.267 (P = 0.023)][a]	[-2.096 (P = 0.036)][a]	-	-	-	-	-	-	-

Notes: [a]Time trend is shown during 20 years (FY2001-FY2020) with statistics Z (P values), based on Cochran–Armitage trend test.

3.2. Factors associated with chronic etizolam use

Comparisons between chronic and non-chronic etizolam users are summarized in Table 2. In multivariable logistic regression analyses, older age, higher initial prescription dose, longer initial prescription duration, and department type were independently associated with chronic etizolam use. In contrast, no significant sex differences were observed. Patients initially prescribed etizolam in internal medicine and surgery-related departments showed higher odds of chronic use than those initially prescribed etizolam in psychiatry.

Table 2
Clinical differences between chronic etizolam users and non-chronic etizolam users, exclusive of the last fiscal-year (2021).

	Logistic regression analyses for 12,519 patients prescribed etizolam during 2001 to 2020[a]			
	Model 1: continuation for ≥ 3 months			
	Chronic	Non-chronic	Odds ratio [95% confidence intervals]	
	(n = 3,981)	(n = 8,538)	Univariate	Multivariate
Age category				
40 years or younger	719 (18.1%)	2,210 (25.9%)	0.779 [0.698, 0.869]	0.745 [0.665, 0.835]
40–60 years	1,086 (27.3%)	2,599 (30.4%)	Reference	Reference
60–75 years	1,295 (32.5%)	2,180 (25.5%)	1.422 [1.288, 1.569]	1.563 [1.409, 1.734]
75 years or older	881 (22.1%)	1,549 (18.1%)	1.361 [1.221, 1.518]	1.705 [1.515, 1.918]
Sex				
Women	2,400 (60.3%)	5,149 (60.3%)	0.999 [0.925, 1.079]	0.955 [0.881, 1.035]
Men	1,581 (39.7%)	3,389 (39.7%)	Reference	Reference
Initially prescribing department				
Internal medicine	1,784 (44.8%)	3,731 (43.7%)	1.226 [1.115, 1.348]	1.051 [0.951, 1.161]
Surgery and others	1,279 (32.1%)	2,453 (28.7%)	1.337 [1.207, 1.480]	1.317 [1.183, 1.467]
Psychiatry	918 (23.1%)	2,354 (27.6%)	Reference	Reference
Initial dose				
0.5 mg/day or less	2,462 (61.8%)	6,170 (72.3%)	Reference	Reference
0.5-1.0mg/day	784 (19.7%)	1,186 (13.9%)	1.657 [1.497, 1.834]	1.604 [1.443, 1.783]
More than 1.0mg/day	735 (18.5%)	1,182 (13.8%)	1.558 [1.406, 1.728]	1.641 [1.471, 1.831]
Initial prescription duration				
3 days or shorter	950 (23.9%)	2,726 (31.9%)	Reference	Reference
3–7 days	629 (15.8%)	2,235 (26.2%)	0.808 [0.720, 0.906]	0.926 [0.822, 1.043]
7–14 days	1,170 (29.4%)	2,339 (27.4%)	1.435 [1.296, 1.589]	1.691 [1.519, 1.882]
Longer than 14 days	1,232 (31.0%)	1,238 (14.5%)	2.856 [2.563, 3.181]	3.116 [2.787, 3.482]
Starting years				
FY2001-2005	1,591 (40.0%)	3,286 (38.5%)	1.234 [1.081, 1.408]	1.454 [1.261, 1.677]
FY2006-2010	1,326 (33.3%)	2,860 (33.5%)	1.181 [1.033, 1.351]	1.233 [1.071, 1.420]
FY2011-2015	677 (17.0%)	1,406 (16.5%)	1.227 [1.057, 1.424]	1.230 [1.054, 1.436]
FY2016-2020	387 (9.7%)	986 (11.6%)	Reference	Reference

Note: [a] Simple and multiple logistic regression analyses were done, regarding "chronic etizolam users (= 1) or non-chronic etizolam users (= 0)" as a dependent variable.

3.3. Sensitivity analyses

Sensitivity analyses using alternative definitions of chronic use (≥ 6 months and ≥ 1 year) yielded broadly similar results (Supplementary Table S1). Older age, higher initial dose, and longer initial prescription duration remained significantly associated with chronic etizolam use across all chronic-use definitions.

3.4. Diagnoses associated with etizolam prescribing

The most frequently recorded indicated diseases associated with etizolam prescribing were insomnia (n = 6,540), anxiety disorder (n = 4,420), depression (n = 3,509), low back pain (n = 3,333), and tension-type headache (n = 2,918). Commonly recorded comorbidities included gastritis (n = 5,694), constipation, and gastric ulcer. Because diagnostic coding was based on administrative insurance records and multiple diagnoses could be assigned to individual patients, these findings should be interpreted descriptively.

4. Discussion

4.1. Principal findings

In this 21-year patient-based cohort study, the number of newly prescribed etizolam users gradually decreased over time, and continuation rates at 3 months, 6 months, and 1 year also significantly declined. These findings suggest that regulatory reforms and increasing awareness regarding benzodiazepine-related risks may have contributed to reductions in long-term etizolam use [6, 8, 10, 14, 15]. However, despite these declining trends, a substantial proportion of patients continued long-term etizolam treatment throughout the study period. Approximately one-third of newly prescribed patients continued treatment for at least 3 months, indicating that chronic etizolam use remains clinically relevant even in recent years. Previous register-based studies have consistently reported that long-term benzodiazepine use remains common despite prescribing restrictions [15]. Our findings extend this literature by demonstrating that reductions in prescription volume do not necessarily translate into equivalent reductions in chronic exposure at the patient level.

Importantly, older age, higher initial prescription dose, and longer initial prescription duration were independently associated with chronic etizolam use. These findings remained broadly consistent across sensitivity analyses using alternative chronic-use definitions.

4.2. Temporal trends and regulatory implications

Several regulatory and guideline-based interventions targeting benzodiazepine prescribing were implemented in Japan during the study period. In particular, the 2016 restriction limiting etizolam prescriptions to 30 days and subsequent reimbursement reforms may have influenced prescribing behaviour [7, 10]. The present findings suggest that these measures may have contributed to gradual reductions in both newly prescribed etizolam users and continuation rates. However, the persistence of chronic users indicates that regulatory interventions alone may be insufficient to completely prevent long-term benzodiazepine exposure.

One possible explanation is that etizolam continues to be prescribed for chronic insomnia, anxiety symptoms, psychosomatic complaints, and pain-related conditions in routine clinical practice [1, 2]. Because etizolam has dual anxiolytic and hypnotic indications, continued prescribing may occur even after prolonged treatment periods.

4.3. Older adults and chronic use

Older age was consistently associated with chronic etizolam use in the present study. This finding is clinically important because older adults are particularly vulnerable to adverse effects associated with benzodiazepine receptor agonists, including falls, fractures, cognitive impairment, and physical dependence [2–4, 16]. Previous meta-analyses have also demonstrated increased risks of adverse events associated with sedative hypnotic use in older adults [17]. Several factors may contribute to prolonged use among older patients [18]. Older adults frequently experience chronic insomnia, anxiety symptoms, somatic complaints, and multimorbidity, which may increase opportunities for repeated prescribing. In addition, deprescribing benzodiazepines in elderly patients may be clinically challenging because withdrawal symptoms and rebound insomnia can complicate discontinuation attempts [19].

These findings underscore the importance of careful medication review and deprescribing strategies in older adults receiving long-term etizolam treatment.

4.4. Initial prescribing characteristics

Higher initial prescription dose and longer initial prescription duration were independently associated with chronic use. These findings suggest that prescribing behaviour at treatment initiation may substantially influence subsequent long-term continuation. This observation may have potential clinical implications because initial prescribing decisions are potentially modifiable. Shorter initial prescriptions and cautious dose selection may help reduce the risk of long-term continuation [20].

Department type was also associated with chronic use. Patients initially prescribed etizolam in non-psychiatric departments showed higher odds of chronic continuation than those initially treated in psychiatry. Although the underlying reasons remain unclear, this

finding may reflect differences in prescribing culture, familiarity with deprescribing strategies, or clinical management priorities between psychiatric and non-psychiatric settings [5, 11, 12].

4.5. Diagnoses associated with etizolam prescribing

Insomnia, anxiety disorder, depression, low back pain, and tension-type headache were commonly recorded as indicated diseases associated with etizolam prescribing. In addition, gastrointestinal conditions such as gastritis, constipation, and gastric ulcer were frequently observed as comorbidities. These findings should be interpreted cautiously because diagnoses were based on administrative insurance records and multiple diagnoses could be assigned to individual patients. Nevertheless, the results suggest that etizolam prescribing frequently occurs in patients with both psychiatric and somatic symptoms, reflecting the broad clinical use of etizolam in routine practice [1].

4.6. Strengths and limitations

This study has several limitations. First, it was conducted at a single tertiary university hospital, which may limit generalizability to other healthcare settings. Second, newly prescribed users were identified within the hospital database, and prescriptions issued at other institutions before referral could not be assessed. Third, the study relied on prescription records and could not determine actual medication adherence or symptom severity. Fourth, diagnoses were based on administrative insurance records and should therefore be interpreted cautiously. Finally, potentially important factors such as concomitant psychotropic medications, socioeconomic factors, physician-level prescribing preferences, and clinical severity were not evaluated.

However, this study also has important strengths. To our knowledge, this is one of the longest patient-based cohort studies examining long-term continuation of etizolam treatment in Japan [6]. The study included more than 12,000 newly prescribed patients over a 21-year period and enabled evaluation of long-term continuation trajectories using a comprehensive electronic medical record database.

5. Conclusions

Although newly prescribed etizolam users and continuation rates gradually decreased over the past two decades, chronic etizolam use remained common in a substantial proportion of patients. Older age, higher initial prescription dose, and longer initial prescription duration were independently associated with chronic continuation.

These findings suggest that reductions in prescription volume alone may not fully capture the persistence of chronic benzodiazepine exposure at the patient level. Careful prescribing at treatment initiation, regular medication review, and deprescribing support [20] may be important for reducing long-term etizolam exposure in routine clinical practice.

Declarations

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Conflicts of Interest

None of the authors (MN, HM, YK, and AN) has any conflicts of interest to declare.

Ethics approval statement

This study was approved by the Ethics Committee of Showa Medical University (approval no. 22-038-A).

Clinical trial number

Not applicable. This study is a clinical trial,

Patient consent statement

This study (opt-out) was publicly disclosed on the university website in accordance with institutional policies.

Permission to reproduce material from other sources

Not applicable.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions

MN: conceptualisation, methodology, data collection, funding acquisition, project administration, resources, writing–original draft, writing–review and editing.

HM: methodology, data collection, writing–original draft.

YK: conceptualisation, writing–original draft, writing.

AN: methodology, data collection, funding acquisition, resources, writing–review and editing.

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Figures

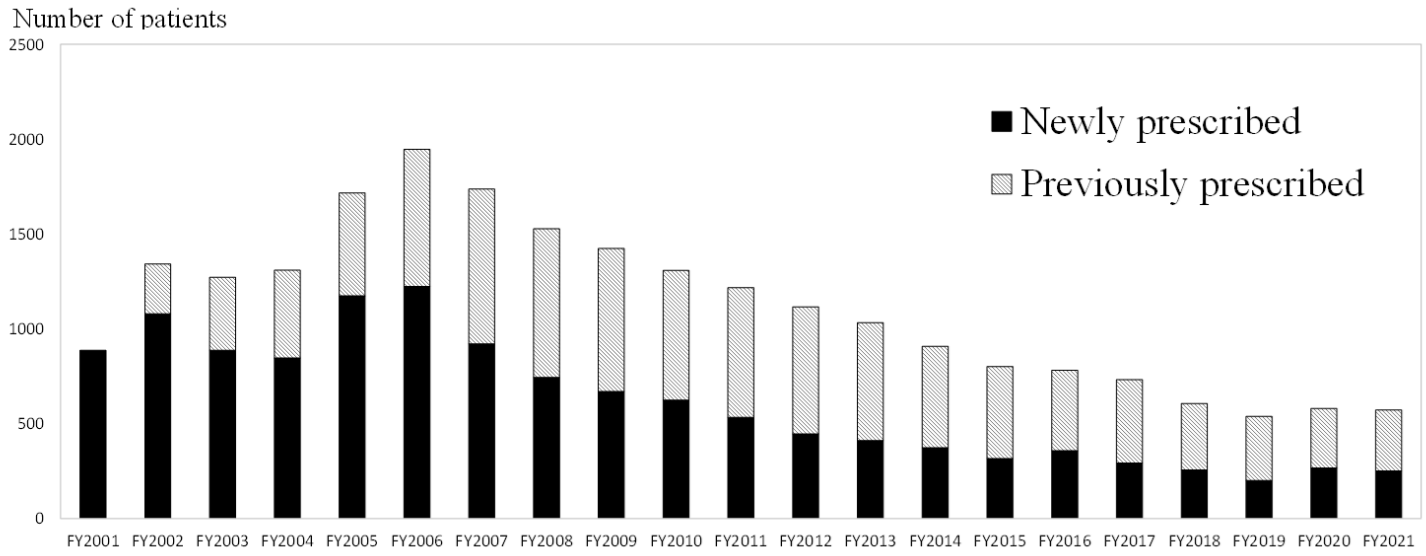


Figure 1

Annual trends in newly and previously prescribed etizolam users

Previously prescribed users represent patients who initiated etizolam in previous fiscal years and continued to receive prescriptions during the corresponding fiscal year.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Supplementarytable2.docx