Observational Study

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# Factors associated with the use of traditional doses of amitriptyline for chronic pain management

## A cross-sectional study

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**Abstract**

There are studies on the effect of low-dose amitriptyline on pain control, but there is a lack of studies on the use of amitriptyline for chronic pain and the factors associated with the prescription of traditional doses. We used a national sample cohort of patients aged ≥ 18 years who were prescribed amitriptyline along with chronic pain, without psychiatric disorders, between 2002 to 2015. We categorized the prescriptions into 2 groups according to the daily dose: low doses (≤25 mg) and traditional doses (>25 mg). Multivariable logistic regression models were used to identify factors associated with traditional dose prescriptions.

Among 177,769 prescriptions for amitriptyline, 15,119 (8.5%) were prescribed for chronic pain. The prevalence of prescriptions and proportion of traditional doses of amitriptyline tended to decrease during the study period. Male sex (odds ratio [OR] 1.09, 95% confidence interval [CI] 1.05–1.13); age 65–80 years (OR 1.12, 95% CI 1.08–1.16), especially ≥ 80 years (OR 1.55, 95% CI 1.45–1.65); headaches (OR 1.18, 95% CI 1.10–1.27), receiving medical aids (OR 2.58, 95% CI 2.46–2.71); and being prescribed benzodiazepines or zolpidem concomitantly (OR 1.10, 95% CI 1.06–1.15) were significantly associated with traditional dose prescriptions of amitriptyline.

Although traditional dose prescriptions of amitriptyline have been declining, close monitoring is still required in the presence of the above-mentioned factors.

**Abbreviations:** CIs = confidence intervals, DNP = diabetic neuropathic pain, ICD-10 = International Classification of Disease, Tenth Revision, LBP = low back pain, NHIS-NSC = National Health Insurance Service-National Sample Cohort, ORs = odds ratios, TCA = tricyclic antidepressant.

**Keywords:** amitriptyline, chronic pain, elderly, headaches, traditional doses

## 1. Introduction

Chronic pain is defined as pain that requires continuous treatment and management, has persisted or recurred for more than 3 months, has a high prevalence, and causes deterioration in the quality of daily life.[1,2] Chronic pain conditions include back pain, fibromyalgia, irritable bowel syndrome, chronic cancer pain, chronic postsurgical and posttraumatic pain, chronic neuropathic pain, chronic headache, and chronic visceral pain.[3] However, chronic pain is a syndrome that is difficult to define as a single characteristic, and it is also a comorbidity of major diseases that increases social burdens, such as coronary artery disease, depression, cardiovascular disease, and cerebrovascular disease. A study showed that chronic pain was related to sociodemographic factors such as older age, female gender, lower socioeconomic status, history of abuse, or interpersonal violence.[4]

Amitriptyline, the most commonly used tricyclic antidepressant (TCA), has been approved for depression, and off-label use is prescribed for several pain conditions, such as headaches, diabetic neuropathic pain, fibromyalgia, and postherpetic neuralgia.[5] It has been used as the first-line therapy for neuropathic pain[2] and as a prophylactic drug for tension-type headache.[6] Additionally, it is commonly used as an alternative or add-on

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*The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.*

*This study protocol was exempt from review by the Institutional Review Board of Chung-Ang University (IRB number:1041078-202002-HR-022-01).*

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therapy for other types of chronic pain.[7] The main mechanism underlying the analgesic effect of amitriptyline involves modulation of norepinephrine and serotonin levels in the synaptic cleft.[8]

However, guidelines, such as the Beers criteria,[9] STOPP/START criteria,[10] and PRISCUS,[11] indicate that the potential risk for cardiac and neurologic adverse effects limits amitriptyline use in elderly patients. Adverse effects, such as arrhythmia,[12,13] seizure,[14] hyponatremia,[15] and anticholinergic effects,[16] have been reported at therapeutic doses used for depression. In particular, QT prolongation[17] and orthostatic hypotension[18] are dose-dependent effects that have triggered studies on low-dose amitriptyline use.

The recommended dose of amitriptyline as an antidepressant is 25 to 300 mg/day; however, a lower dose is used for chronic pain. Studies have demonstrated the effectiveness and safety of amitriptyline doses for chronic pain: lower back pain at 25 mg/day,[19] chronic neck pain at 5 mg/day,[20] and chest pain at 10 mg/day.[21] Recent studies on the clinical use of amitriptyline for chronic pain have shown that it is effective and well tolerated, with minimal risk of adverse events.[19,21]

Nevertheless, studies on the real-world utilization of amitriptyline and associated factors to be considered during drug intervention are lacking. Therefore, we used real-world data to assess the prevalence of amitriptyline prescriptions according to dose and examined the factors associated with the prescription of higher doses of amitriptyline, which may lead to potential adverse reactions.

## 2. Methods and materials

### 2.1. Data source

This cross-sectional study was used the nationwide cohort database of the National Health Insurance Service-National Sample Cohort (NHIS-NSC) in South Korea (data number: NHIS-2020-2-092). The NHIS-NSC database was designed to provide medical history and treatment information for the entire sample by extracting a nationwide sample, a dataset consisting of approximately 2% of the general Korean population. The NHIS-NSC database consists of anonymized demographic information, medical institution information, diagnosis codes, socioeconomic status, drug prescriptions, and patient health records. This study protocol was exempt from review by the Institutional Review Board of Chung-Ang University (IRB number:1041078–202002-HR-022-01).

### 2.2. Study population

For our analysis, we enrolled adults in the NHIS-NSC database aged 18 years or older who were prescribed amitriptyline at least once (WHO ATC code N06AA09) between 2002 and 2015. Using the International Classification of Disease, Tenth Revision (ICD-10), we excluded those with 1 or more diagnoses of psychiatric disease (F00-F99) to limit the study population to patients who used amitriptyline for nonpsychiatric reasons. The diagnosis of chronic pain for the same claim with an amitriptyline prescription was assessed and classified as headache,[22] diabetic neuropathic pain (DNP), low back pain (LBP),[23] or other chronic pain. Chronic pain was defined using the ICD-10. DNP patients were considered those diagnosed with diabetes mellitus (E10-E14).[24] Other chronic pain included abdominal and bowel pain; central pain syndrome; fibromyalgia; musculoskeletal chest pain; neck pain; noninflammatory arthritic disorders; orofacial, ear, and temporomandibular pain disorders; and urogenital, pelvic, and menstrual pain.[25–27] The ICD-10 codes are listed in Table S1, Supplemental Digital Content, http://links.lww.com/MD/L211.

### 2.3. Operational definition of amitriptyline doses

We calculated the daily dose of amitriptyline and categorized the prescriptions into 2 groups by daily dose as follows: low-doses (≤25 mg daily) and traditional doses (>25 mg daily).[19,28] In addition, the prevalence of low-dose amitriptyline prescriptions was further assessed by dividing the dose range into < 10 mg and 10 to 25 mg[29] considering that the guidelines recommend initiating treatment with a low-dose of amitriptyline.

### 2.4. Factors associated with the use of traditional doses of amitriptyline

The data collected in this study comprised information on patient characteristics; sociodemographic factors, including age, sex, insurance type (national health insurance or medical aid), type of medical institution, geographic region (Seoul, metropolitan, and rural area), physician specialty, and prescription year. To analyze cardiovascular disease as a potentially associated factor requiring attention in people using amitriptyline, we collected data on drugs prescribed for hypertension,[30] heart failure,[31] and arrhythmia,[32] described in the same prescription as that of amitriptyline (Table S2, Supplemental Digital Content, http://links.lww.com/MD/L212). As benzodiazepines and zolpidem can potentially increase the risk of falls when combined with amitriptyline,[33] we also collected data on benzodiazepines or zolpidem when prescribed with amitriptyline (Table S3, Supplemental Digital Content, http://links.lww.com/MD/L213). In addition to headache, DNP, LBP, fibromyalgia,[34] and osteoarthritis[35] were added as independent variables to identify factors associated with the use of amitriptyline at traditional doses.

### 2.5. Statistical analyses

Patient and provider characteristics, including frequency and proportion, are presented using descriptive statistics. From 2002 to 2015, the number of people was determined by year and amitriptyline prescription dose group. In the preliminary analysis, patients diagnosed with headache, DNP, and LBP had a high prevalence of amitriptyline prescription. Therefore, we analyzed the age- and sex-standardized prevalence of amitriptyline use among these patients, as a standard population diagnosed with each pain condition in 2015, from the NHIS-NSC database. The Spearman correlation coefficient was used to measure the association between amitriptyline use and calendar year for chronic pain diseases. We compared the change in the distribution of the amitriptyline dose groups among the 3 pain conditions. Multivariable logistic regression models were used to identify factors associated with traditional dose prescriptions. Variables that were associated with traditional doses ($P < .1$ in the univariate model) were included in a multivariable model; these variables were then checked for multicollinearity. Subgroup analyses were performed to investigate the risk of traditional amitriptyline doses for inpatients and outpatients.

The model fit was assessed using the Hosmer–Lemeshow goodness-of-fit test and C-statistic. Finally, we calculated the odds ratios (ORs) and 95% confidence intervals (CIs) for sex, age, type of insurance, type of medical institution, physician specialty, prescription year, chronic pain conditions, co-diagnosis, and benzodiazepine and zolpidem as co-medications. Statistical analyses were performed using SAS version 9.4 (SAS Institute, Inc., Cary, NC).

## 3. Results

Of the 128,017 patients who were prescribed amitriptyline, 43,707 diagnosed with psychiatric disorders were excluded from the analysis. Among the remaining patients, 1172 aged < 18 years and 36,338 with non-chronic pain conditions

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were excluded, resulting in a final study population of 46,249 (Fig. 1).

We analyzed the annual characteristics of the study population but have only shown the characteristics recorded in 3 years:2002, the beginning year, 2015 as the last year; and 2007, with the highest number of amitriptyline prescriptions (Table 1). The 40 to 64 years age group accounted for the largest proportion, followed by the 65 to 79 years age group. The proportion of patients aged 65 to 79 and over 80 years increased from 24.59% and 2.10% in 2002 to 31.63% and 7.81% in 2015, respectively. Throughout the study period, female patients (60% or more), patients from rural areas (59% or more), outpatients (85% or more), and patients prescribed by clinics (45% or more) accounted for a large proportion of the study population. The patients who visited internal medicine units accounted for the largest proportion, followed by those admitted to Neurology and Orthopedic units.

### 3.1. Trends of prevalence of amitriptyline by chronic pain diseases

When comparing the 3 types of pain diseases, it was observed that the age- and sex-standardized prevalence percentages of amitriptyline prescriptions among patients diagnosed with headache plateaued (Spearman correlation coefficient = −0.524, $P = .055$) but decreased significantly among patients diagnosed with LBP (Spearman correlation coefficient = −0.987, $P < .001$) and DNP (Spearman correlation coefficient = −0.996, $P < .001$) (Fig. 2).

As shown in Figure 3, the prescription rate of traditional doses of amitriptyline decreased for all 3 pain-related diseases. The proportion of traditional dose prescriptions of amitriptyline decreased from 23.7% in 2002 to 6.3% in 2015 among LBP patients, with the largest proportion observed at 17.4% in 2007. As of 2015, the proportion of traditional dose prescriptions was lower among DNP (3%) and LBP (5%) patients and was only 3.3% among patients with headache. The increase in the rate of low-dose ( < 10 mg) prescriptions was the largest in patients with headaches, from 14.9% in 2002 to 38.2% in 2015.

### 3.2. Factors associated with traditional dose prescriptions of amitriptyline

Table 2 shows the factors associated with the prescription of traditional amitriptyline doses. The results of multivariable analyses revealed that male (OR 1.09, 95% CI 1.05–1.13); older, especially those over the age of 80 years (OR 1.55, 95% CI 1.45–1.65); and medical aid patients (OR 2.58, 95% CI 2.46–2.71) were more likely to be prescribed amitriptyline at the traditional doses. Regarding the factors associated with medical institutions, inpatients (OR 2.11, 95% CI 2.00–2.23), and patients who visited hospitals (OR 1.06, 95% CI 1.01–1.10) and neurosurgery departments (OR 1.31, 95% CI 1.22–1.42) were more likely to be associated with traditional dose prescriptions of amitriptyline. Furthermore, patients diagnosed with headache (OR 1.18, 95% CI 1.10–1.27) were more likely to be prescribed amitriptyline at traditional doses. In contrast, patients who visited neurology (OR 0.55, 95% CI 0.51–0.60), underwent rehabilitation (OR 0.64, 95% CI 0.58–0.71), had DNP (OR 0.88, 95% CI 0.82–0.93) and arthritis (OR 0.84, 95% CI 0.78–0.90) as their chronic pain diagnoses, and had hypertension (OR 0.82, 95% CI 0.79–0.86) as a comorbidity were less likely to be prescribed traditional doses of amitriptyline. Patients receiving benzodiazepines or zolpidem (OR 1.10, 95% CI 1.06–1.15) were more likely to be prescribed traditional doses of amitriptyline. Notably, the prescription of traditional doses of amitriptyline decreased over time (OR 0.86, 95% CI 0.85–0.86).

The results of subgroup analysis are shown in Figure 4. In outpatients, an increased association with traditional doses of amitriptyline was observed in older patients, especially over the age of 80 years (OR 1.69, 95% CI 1.58–1.82), headache (OR 1.25, 95% CI 1.16–1.35), and patients with arrhythmia (OR 1.34, 95% CI 1.06–1.70). In contrast, in inpatients, an increased association with traditional doses of amitriptyline was observed in the age group of 18 to 40 years (OR 1.21, 95% CI 1.02–1.43); patients with DNP (OR 1.53, 95% CI 1.28–1.82) or fibromyalgia (OR 2.53, 95% CI 1.18–5.40); patients treated in orthopedics (OR 1.77, 95% CI 1.48–2.11), neurosurgery (OR 2.47, 95% CI 2.05–2.98), or GP/family medicine

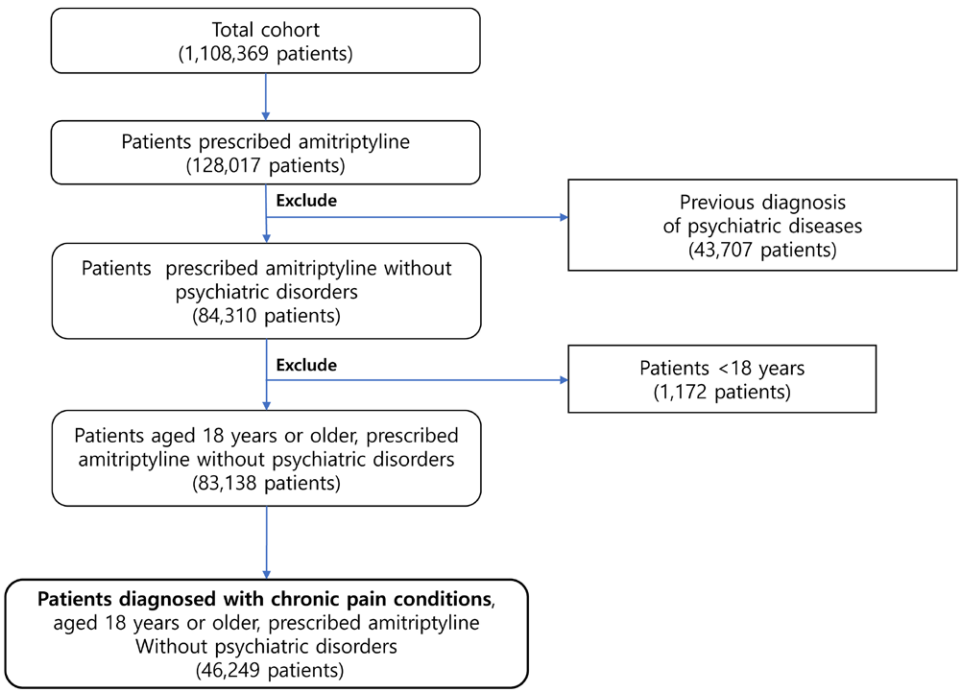


**Figure 1.** Flow chart of the study population of descriptive study.

**Table 1**

**Characteristics of patients prescribed amitriptyline, 2002, 2007 and 2015.**

| | 2002 (N = 3379) | | 2007 (N = 5418) | | 2015 (N = 4739) | |
|---|---|---|---|---|---|---|
| | n | (%) | n | (%) | n | (%) |
| Age, yr | | | | | | |
| Mean(±SD) | 54.07 (±14.55) | | 57.09 (±15.23) | | 58.53 (±15.90) | |
| 18–39 | 601 | (17.79) | 789 | (14.56) | 655 | (13.82) |
| 40–64 | 1876 | (55.52) | 2586 | (47.73) | 2215 | (46.74) |
| 65–79 | 831 | (24.59) | 1765 | (32.58) | 1499 | (31.63) |
| ≥80 | 71 | (2.10) | 278 | (5.13) | 370 | (7.81) |
| Sex | | | | | | |
| Male | 1081 | (31.99) | 1960 | (36.18) | 1784 | (37.65) |
| Female | 2298 | (68.01) | 3458 | (63.82) | 2955 | (62.35) |
| Type of insurance | | | | | | |
| Medical insurance | 3226 | (95.47) | 4946 | (91.29) | 4408 | (93.02) |
| Medical aid | 153 | (4.53) | 472 | (8.71) | 331 | (7.15) |
| Geographic region | | | | | | |
| Seoul | 530 | (15.69) | 831 | (15.34) | 691 | (14.58) |
| Metropolitans | 737 | (21.81) | 1204 | (22.22) | 1209 | (25.51) |
| Rural area | 2112 | (62.50) | 3383 | (62.44) | 2839 | (59.91) |
| Setting of amitriptyline prescription | | | | | | |
| Inpatients | 286 | (8.27) | 704 | (12.66) | 698 | (14.20) |
| Outpatients | 3171 | (91.73) | 4855 | (87.34) | 4218 | (85.80) |
| Type of institution | | | | | | |
| Tertiary hospital | 497 | (14.42) | 592 | (10.61) | 422 | (8.81) |
| Hospital | 557 | (16.16) | 1726 | (30.94) | 2119 | (44.26) |
| Clinics | 2392 | (69.41) | 3144 | (56.36) | 2196 | (45.86) |
| Public health | 0 | (0.00) | 116 | (2.08) | 51 | (1.07) |
| Physician specialty | | | | | | |
| Internal medicine | 1236 | (35.26) | 1910 | (33.67) | 1345 | (27.22) |
| Neurology | 496 | (14.15) | 997 | (17.57) | 1254 | (25.37) |
| Orthopedics | 972 | (27.73) | 1469 | (25.89) | 1097 | (22.20) |
| Neurosurgery | 256 | (7.30) | 472 | (8.32) | 502 | (10.16) |
| GP/family medicine | 132 | (3.77) | 231 | (4.07) | 168 | (3.40) |
| Rehabilitation | 223 | (6.36) | 330 | (5.82) | 276 | (5.58) |
| Others | 190 | (5.42) | 264 | (4.65) | 300 | (6.07) |
| Comorbidities* | | | | | | |
| Hypertension | 888 | (24.67) | 2401 | (43.42) | 2177 | (45.18) |
| Arrhythmia | 44 | (1.3) | 157 | (2.88) | 85 | (1.79) |
| Co-medications† | | | | | | |
| Benzodiazepine or zolpidem | 1383 | (38.32) | 2087 | (35.29) | 1391 | (29.35) |

GP = general practitioner, SD = standard deviation.

* Comorbidity exposure was measured from 365 days before the amitriptyline prescription date.

† Co-medication exposure was measured from 28 days before the amitriptyline prescription date to the prescription end date.

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(OR 1.94, 95% CI 1.49–2.53) units; and patients prescribed benzodiazepines or zolpidem (OR 1.40, 95% CI 1.26–1.57) as co-medications.

## 4. Discussion

Our study showed that the prescription of traditional doses of amitriptyline gradually decreased over the years and was associated with male sex, older age, medical aid, inpatient settings, amitriptyline prescriptions from neurosurgery or orthopedic units, headaches, and prescriptions of benzodiazepines or zolpidem as co-medications.

As a mechanism of action for analgesia, amitriptyline not only modulates norepinephrine and serotonin – its primary mechanisms in treating depression – but also serves as a blocker or activator of ion channels, including sodium channel blocking, calcium channel blocking, and potassium channel activation. Additionally, it enhances adenosine availability and local release, boosts the function of $GABA_B$ receptors, and influences the production of $PGE_2$ and reduction of TNF α. These various actions collectively contribute to pain control.[7,8]

The pattern of decline in amitriptyline use observed in this study was related to the introduction of new drugs or clinical treatment guidelines. In Korea, gabapentin and pregabalin were approved in 2005, and several studies[36,37] have shown that they are effective in treating neuropathic pain. In addition, the 2005 EFNS guidelines recommend gabapentin, pregabalin, and TCAs for the treatment of neuropathy.[2] This could be the reason for the decrease in amitriptyline prescriptions since 2007. However, there was no significant change in the number of amitriptyline prescriptions for the treatment of headache. This could be because current treatment guidelines recommend amitriptyline as the main preventive agent for tension-type headaches.[6] The decrease in the prescription of traditional doses in our study was consistent with recent recommendations for chronic pain conditions.[28,38] Recent studies have suggested that low-dose amitriptyline is as effective as high-dose amitriptyline, with fewer adverse effects, even in patients with DNP[38] and headache.[28] Low doses of ≤ 25 mg/day accounted for more than 90% of amitriptyline prescriptions in 2015, and the annual increase in the proportion of low doses of < 10 mg in our study reflects the efforts to treat pain while minimizing adverse reactions to amitriptyline.

The main factors associated with the use of traditional amitriptyline doses were male sex, older age, medical aid, inpatient settings, amitriptyline prescriptions from neurosurgery or orthopedic units, headache, and prescriptions of benzodiazepines or zolpidem as co-medications.

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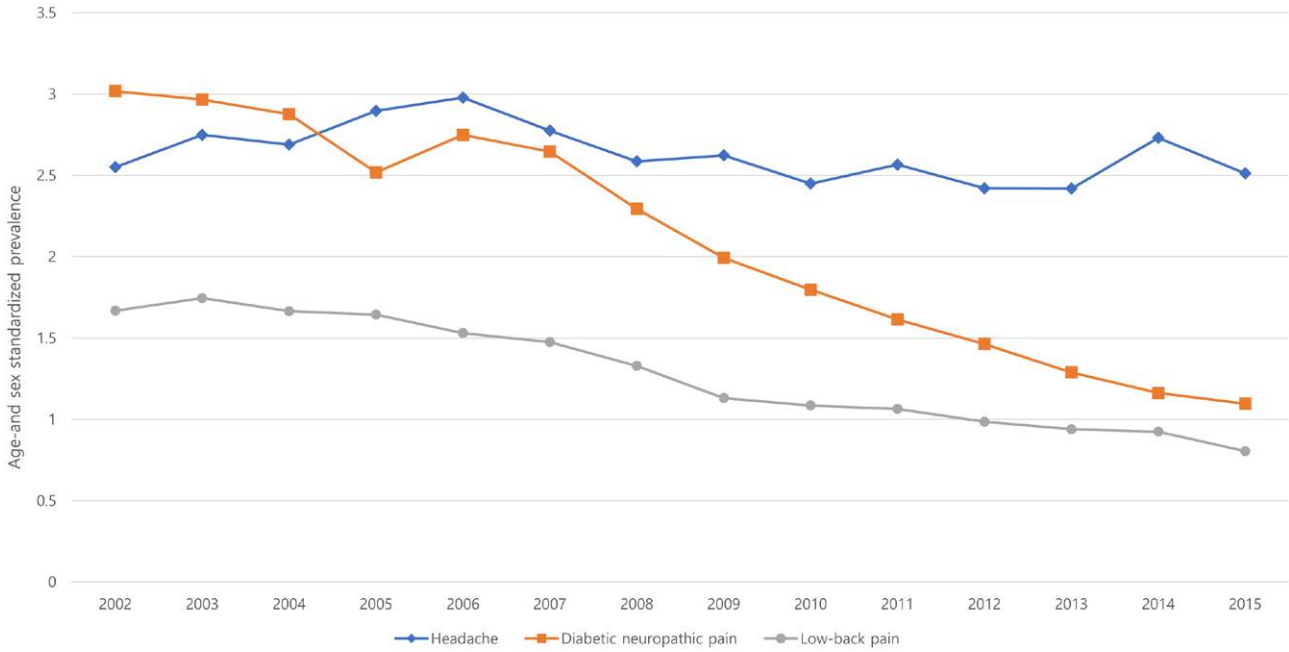


**Figure 2.** Age- and sex-standardized prevalence of patients prescribed amitriptyline, grouped according to pain diseases in Korea (2002–2015).

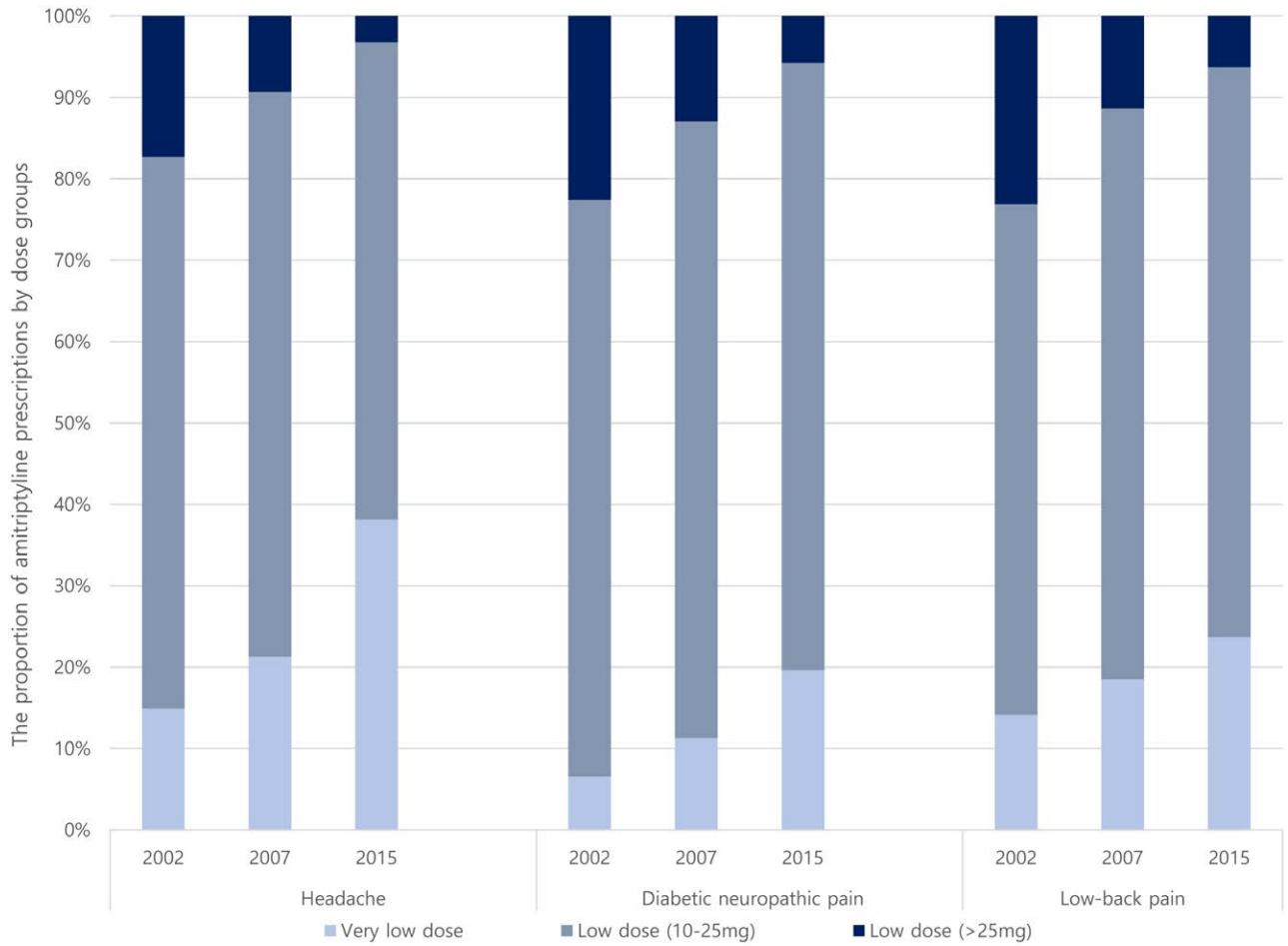


**Figure 3.** Trends in the proportion of amitriptyline dosing in three pain diseases in Korea (2002–2015).

Male sex was significantly associated with the use of traditional doses of amitriptyline, which was inconsistent with previous findings of a higher prevalence of chronic pain[39] and severe pain[40] in female patients. However, the use of

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**Table 2**

**Factors associated with the prescriptions of traditional doses of amitriptyline, 2002–2015.**

| | Low dose Amitriptyline (N = 162,610) | | Traditional dose amitriptyline (N = 15,159) | | Univariate analysis | | | Multivariable analysis | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | N | (%) | N | (%) | OR | (95% CI) | | OR | (95% CI) | |
| Sex | | | | | | | | | | |
| Female | 101,654 | (62.51) | 9302 | (61.36) | ref | | | ref | | |
| Male | 60,956 | (37.49) | 5857 | (38.64) | 1.05 | (1.02, | 1.09) | 1.09 | (1.05, | 1.13) |
| Age | | | | | | | | | | |
| Mean (±SD) | 60.97 (±14.14) | | 61.05 (±14.61) | | | | | | | |
| 18–40 | 13,742 | (8.45) | 1347 | (8.89) | 1.09 | (1.03, | 1.16) | 1.04 | (0.97, | 1.11) |
| 40–64 | 74,750 | (45.97) | 6715 | (44.30) | ref | | | ref | | |
| 65–80 | 63,009 | (38.75) | 5801 | (38.27) | 1.03 | (0.9, | 1.06) | 1.12 | (1.08, | 1.16) |
| ≥80 | 11,109 | (6.83) | 1296 | (8.55) | 1.30 | (1.22, | 1.38) | 1.55 | (1.45, | 1.65) |
| Type of insurance | | | | | | | | | | |
| Medical insurance | 148,945 | (91.60) | 12,510 | (82.53) | ref | | | ref | | |
| Medical aid | 13,656 | (8.40) | 2649 | (17.47) | 2.31 | (2.21, | 2.42) | 2.58 | (2.46, | 2.71) |
| Geographic region | | | | | | | | | | |
| Seoul | 21,849 | (13.44) | 1883 | (12.42) | ref | | | ref | | |
| Metropolitan | 39,656 | (24.39) | 3888 | (25.65) | 1.14 | (1.07, | 1.21) | 1.07 | (1.00, | 1.13) |
| Rural area | 101,105 | (62.18) | 9388 | (61.93) | 1.08 | (1.02, | 1.13) | 1.02 | (0.97, | 1.08) |
| The setting of amitriptyline prescription | | | | | | | | | | |
| Outpatient | 150,279 | (92.42) | 12,889 | (85.03) | ref | | | ref | | |
| Inpatient | 12,331 | (7.58) | 2270 | (14.97) | 2.15 | (2.05, | 2.25) | 2.11 | (2.00, | 2.23) |
| Type of Institution | | | | | | | | | | |
| Tertiary care hospital | 15,288 | (9.40) | 1258 | (8.30) | 0.88 | (0.83, | 0.94) | 0.95 | (0.89, | 1.01) |
| Hospital | 45,200 | (27.80) | 4356 | (28.74) | 1.03 | (1.00, | 1.07) | 1.06 | (1.01, | 1.10) |
| Clinics | 100,217 | (61.63) | 9342 | (61.63) | ref | | | ref | | |
| Public health center | 1905 | (1.17) | 203 | (1.34) | 1.14 | (0.99, | 1.32) | 0.90 | (0.77, | 1.06) |
| Physician specialty | | | | | | | | | | |
| Internal medicine | 69,254 | (42.59) | 6085 | (40.14) | ref | | | ref | | |
| Neurology | 22,813 | (14.03) | 1166 | (7.69) | 0.58 | (0.55, | 0.62) | 0.55 | (0.51, | 0.60) |
| Orthopedics | 38,927 | (23.94) | 4233 | (27.92) | 1.24 | (1.19, | 1.29) | 1.20 | (1.13, | 1.27) |
| Neurosurgery | 10,198 | (6.27) | 1380 | (9.10) | 1.54 | (1.45, | 1.64) | 1.31 | (1.22, | 1.42) |
| GP/family medicine | 5799 | (3.57) | 609 | (4.02) | 1.20 | (0.10, | 1.31) | 1.19 | (1.08, | 1.31) |
| Rehabilitation | 8831 | (5.43) | 548 | (3.62) | 0.71 | (0.65, | 0.77) | 0.64 | (0.58, | 0.71) |
| Others | 6788 | (4.17) | 1138 | (7.51) | 1.91 | (1.78, | 2.04) | 1.82 | (1.70, | 1.97) |
| Type of chronic pain | | | | | | | | | | |
| Headache | 24,832 | (15.27) | 2002 | (13.21) | 0.84 | (0.80, | 0.89) | 1.18 | (1.10, | 1.27) |
| DNP | 56,799 | (34.93) | 5016 | (33.09) | 0.92 | (0.89, | 0.95) | 0.88 | (0.82, | 0.93) |
| LBP | 48,633 | (29.91) | 5183 | (34.19) | 1.22 | (1.18, | 1.26) | 1.05 | (0.99, | 1.11) |
| Fibromyalgia | 1013 | (0.62) | 40 | (0.26) | 0.42 | (0.31, | 0.58) | 0.77 | (0.56, | 1.07) |
| Arthritis | 14,977 | (9.21) | 1428 | (9.42) | 1.03 | (0.97, | 1.09) | 0.84 | (0.78, | 0.90) |
| Co-diagnosis* | | | | | | | | | | |
| Hypertension | 47,653 | (29.31) | 3948 | (26.04) | 0.85 | (0.82, | 0.88) | 0.82 | (0.79, | 0.86) |
| Arrhythmia | 803 | (0.49) | 102 | (0.67) | 1.37 | (1.11, | 1.68) | 1.15 | (0.93, | 1.42) |
| CHF | 1872 | (1.15) | 176 | (1.16) | 1.01 | (0.86, | 1.18) | | | |
| Co-medications† | | | | | | | | | | |
| Benzodiazepine or zolpidem | 30,498 | (18.76) | 3399 | (22.42) | 1.25 | (1.20, | 1.30) | 1.10 | (1.06, | 1.15) |
| Calendar year | | | | | | | | | | |
| Mean (±SD) | 2009.3 | (±3.74) | 2007.4 | (±3.62) | 0.87 | (0.87, | 0.88) | 0.86 | (0.85, | 0.86) |

CHF = congestive heart failure, CIs = confidence intervals, DNP = diabetic neuropathic pain, GP = general practitioner, LBP = low back pain, OR = odds ratio, SD = standard deviation.

* Co-diagnosis was a diagnosis identified in the same claim with amitriptyline prescription.

† Co-medications were drugs identified in the same claim with amitriptyline prescription.

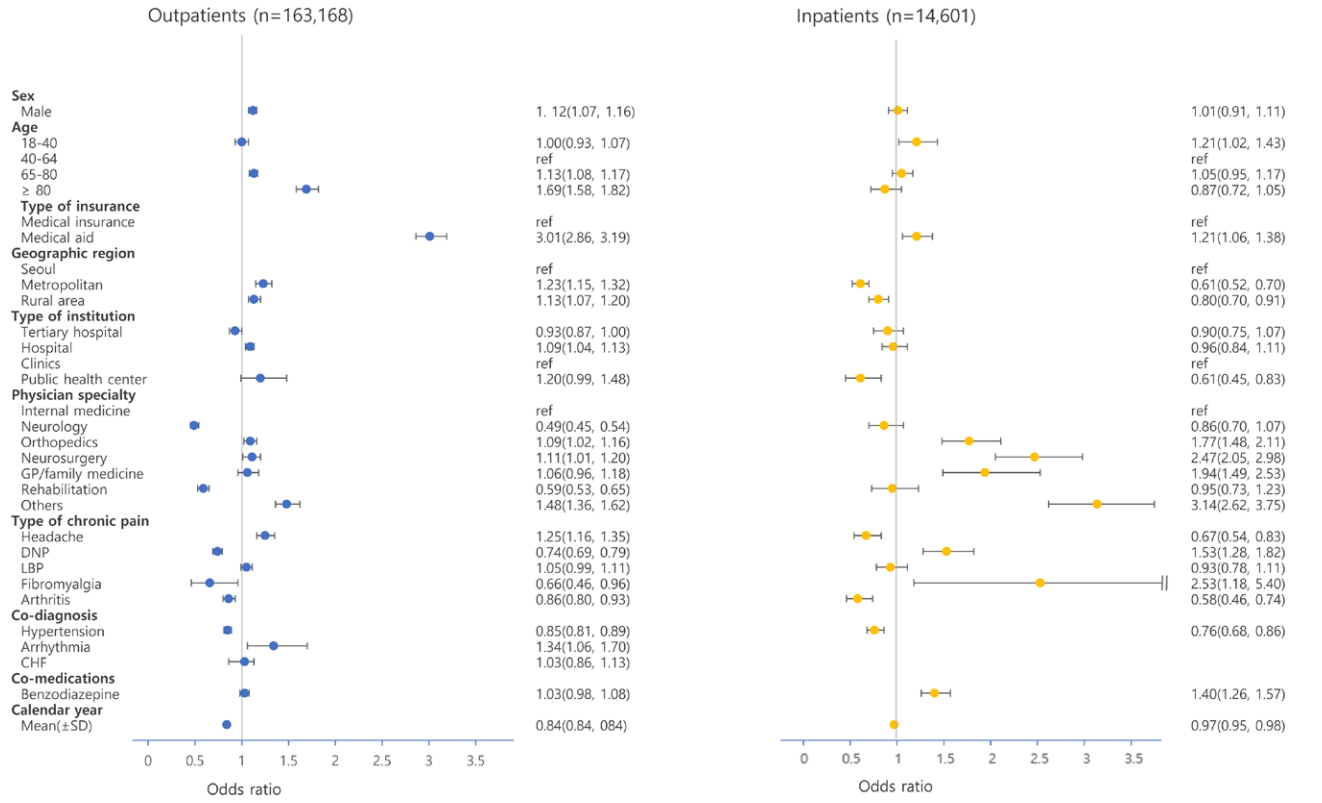


**Figure 4.** Subgroup analysis of factors associated with traditional dose prescription of amitriptyline according to hospital settings among amitriptyline prescriptions for chronic pain, 2002–2015.

amitriptyline at doses higher than the traditional doses is recommended for prophylaxis of headache,[6] and the prevalence of headache is 3 times higher in male patients than in female patients.[41]

The association between the use of traditional doses of amitriptyline in elderly patients and patients prescribed benzodiazepines or zolpidem highlights the safety concerns associated with the use of amitriptyline. Since amitriptyline can induce several anticholinergic adverse reactions and increase the risk of falls, several studies[42,43] and the Beers and STOPP/STAR criteria recommend that elderly people avoid using amitriptyline.[9,10] As benzodiazepines are also drugs that increase the risk of falls, their co-administration with amitriptyline could further increase the risk of falls.[33] It is particularly noteworthy that the use of traditional doses of amitriptyline increases with age.

Low socioeconomic status was also associated with a higher prevalence of the use of traditional doses of amitriptyline. In contrast to our results, a previous study showed that socioeconomic status did not influence the selection of TCAs and other antidepressants in patients with depression.[44] However, unlike previous studies, our study targeted patients with chronic pain, and amitriptyline is less expensive than gabapentin or pregabalin,[45] which are widely used for chronic pain. In Korea, the use of gabapentin and pregabalin is reimbursed to some extent for neuropathic pain and fibromyalgia.[46]

The results of this study are consistent with the treatment guidelines for each pain condition. The guidelines recommend 10 to 100 mg/day of amitriptyline for the prevention of migraine and tension-type headache,[6] and 75 mg/day for reducing headache recurrence.[47] Indeed, there was a significantly high correlation between the use of traditional doses of amitriptyline and headache in outpatients, because amitriptyline is used for the prophylaxis of migraine or tension-type headache.[6] However, for DNP, although the effective dose of amitriptyline is 75 mg/day, guidelines recommend gradually increasing the dose from a low-dose of 10 to 25 mg/day.[29] Although arthritis is not mentioned in the guidelines, it is presumed that many studies on chronic pain have investigated the use of low-doses of amitriptyline for arthritis.[48]

In our study population, hypertension was less likely to be associated with the use of traditional doses of amitriptyline, which could be attributed to adverse cardiovascular reactions.[49] However, in the subgroup analysis of outpatients, the association with traditional doses of amitriptyline was high in patients with arrhythmia, indicating the need to pay more attention to the cardiovascular adverse effects of amitriptyline in these patients. The previous study has shown an association between QTc prolongation and dose-response of amitriptyline.[17] A recent study also suggested that cardiovascular adverse events should be carefully considered when using TCAs in the elderly.[50]

Patients who visited neurology or rehabilitation clinics, patients with DNP, and arthritis as their chronic pain diagnoses were less likely to be prescribed a traditional dose of amitriptyline. The results of patients who visited the neurology department or rehabilitation department were consistent with the results of previous studies.[19,20,51] Previous studies of TCAs, such as low-dose amitriptyline and pain, have focused on pain conditions addressed in neurology and rehabilitation medicine, such as chronic back pain,[19] fibromyalgia,[50] and neck pain.[20] DNP is considered to reflect a guideline recommending a low-dose,[29] and the results are consistent with studies showing that a low dose of amitriptyline is effective for osteoarthritis, even in arthritis.[52]

Traditional doses of amitriptyline were used for severe pain in patients treated in surgery departments, such as neurosurgery and orthopedics, who were also taking benzodiazepines as co-medications. These results are consistent with those of the previous studies. Amitriptyline is helpful for pain control before and after spinal surgery,[53] and the use of benzodiazepines is associated with severe pain.[54] The higher association with the use

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of traditional doses of amitriptyline in inpatients than in outpatients may also be due to pain severity. The use of traditional doses of amitriptyline is linked to safety issues, but this risk can be lowered by monitoring electrocardiogram changes[55] or serum sodium concentrations[56] in an inpatient setting. However, further research is needed to determine whether the use of traditional doses affects the occurrence of the adverse effects of amitriptyline.

This study has several strengths. First, this is the first study to examine the use of amitriptyline for pain control over 13 years, using a large-scale, representative database. While this study showed the use of amitriptyline in patients with chronic pain without psychiatric disorders, studies have been conducted on the prescription of amitriptyline for depressive patients.[57,58] In particular, we compared the use of amitriptyline for various pain-related diseases. Second, in patients with chronic pain using amitriptyline, different trends were detected when classifying by dose and factors associated with the use of traditional doses of amitriptyline. Finally, selection bias was minimized by using a nationwide cohort database, which increased the generalizability of the results. This generalizability, which can be applied not only to Korea but also to other countries, can be applied.

This study had some limitations. First, there was a lack of validation of the diagnosis code for chronic pain using ICD-10 codes. As it tends to be used to facilitate billing services, physicians may not reflect all of the patient's conditions. Second, in the study of factors associated with the traditional dose of amitriptyline, patients with DNP were considered to be diagnosed with diabetes among patients prescribed amitriptyline, but the possibility of its use for pain other than diabetic neuropathy could not be ruled out. Third, all medications associated with falls were excluded. In our study, benzodiazepine was the most commonly used drug among the psychotropic medications that cause falls in the elderly,[33,59] and zolpidem is a drug with increasing evidence related to falls.[33] Rather than looking for drugs that can cause more falls when used in combination with TCAs, it is important to confirm that patients prescribed benzodiazepines and zolpidem need more attention regarding the risk of falls, because they tend to prescribe traditional doses of amitriptyline. Fourth, we included prescriptions for patients diagnosed with chronic pain, but it could not be determined whether these treatments were used to induce sleep[60] or for depression without indications of psychiatric diseases. Furthermore, it is possible that patients with psychiatric disorders visited medical institutions for reasons other than obtaining amitriptyline prescriptions. Finally, because only the prescription pattern was available, it was not possible to confirm whether the patients took the drug.

Our study found that the prevalence of prescriptions and proportion of traditional doses of amitriptyline tended to decrease during the study period, 2002 to 2015. Potential causative factors associated with traditional doses of amitriptyline were old age, male sex, receiving medical aid, and being prescribed benzodiazepines or zolpidem concomitantly, except for the severity of pain. Therefore, close attention should be paid to the use of amitriptyline to avoid high doses that can cause potential adverse reactions. Furthermore, future research should focus on elucidating the risks associated with traditional doses of amitriptyline.

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## Author contributions

**Conceptualization:** Hyunji Koo, Sun-Young Jung.
**Writing – original draft:** Hyunji Koo.
**Writing – review & editing:** Kyeong Hye Jeong, Nakyung Jeon, Sun-Young Jung.

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