BPB Reports

Report

Treatment Disruption Associated with Amitriptyline Shortage in Routine Clinical Practice: A Retrospective Descriptive Study

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Received June 2, 2026; Accepted August 6, 2026

Objective: To describe amitriptyline treatment modifications during a supply-restriction period and evaluate changes in pain intensity in an exploratory analysis. Methods: This single-center retrospective study included adults prescribed amitriptyline for pain management between January and December 2022 who remained on treatment when prescribing restrictions began in April 2023. Discontinuation or switching was assessed through March 2024. The primary endpoint was the proportion of patients who discontinued amitriptyline or switched to another drug for any reason. Treatment modifications were classified as either documented shortage-related or attributable to other clinical reasons. Numerical Rating Scale (NRS) changes were explored among shortage-related cases with paired baseline and 8-week assessments. Results: Of 180 patients screened, 83 were included. During the observation period, 81 patients (97.6%) underwent treatment modification for any reason, and 52 of 83 (62.7%) had treatment modifications explicitly documented as shortage-related. The remaining 29 modifications were attributed to inadequate pain control and/or adverse events. Among the 52 shortage-related cases, paired NRS scores were available for 33 patients. Median NRS scores were 5 [interquartile range (IQR), 3–7] at baseline and 5 [IQR, 4–6] at 8 weeks, with no significant overall change (p = 0.21). Changes did not differ significantly between the discontinuation and switching groups (p = 0.48). All patients with paired NRS scores were treated in the Department of Anesthesiology. Conclusions: Documented shortage-related treatment modification occurred in approximately two-thirds of eligible patients. The NRS findings were exploratory and should be interpreted cautiously because of potential selection bias.

Key words Amitriptyline, Drug shortages, Neuropathic pain, Pain management, Treatment modification

INTRODUCTION

Since 2020, repeated manufacturing irregularities and quality control issues among generic drug manufacturers in Japan have caused persistent pharmaceutical supply shortages.[1,2] These shortages have affected routine clinical practice by disrupting the continuity of pharmacotherapy and requiring treatment modification in many patients. Drug shortages have become a global healthcare issue, and previous studies have suggested that supply instability may affect patient management, treatment modification, and healthcare resource utilization.[3-5] However, the practical consequences of drug shortages in routine practice have not been sufficiently investigated in Japan.

Amitriptyline is the only tricyclic antidepressant approved for the management of peripheral neuropathic pain in Japan and is recommended as a first-line treatment in Japanese clinical guidelines.[6] The first notice of limited amitriptyline shipment was issued in March 2023 because of reduced manufacturing capacity, followed by a second notice in May 2023. At Fukuoka University Hospital, prescribing restrictions were implemented beginning in April 2023; outpatient prescriptions were temporarily discontinued, and inpatient use was restricted. Accordingly, this study focused on treatment modifications that occurred during the supply-restriction period from April 2023 through March 2024.

In this study, we aimed to describe treatment modifications associated with amitriptyline supply shortages and exploratorily evaluate changes in pain scores in routine clinical practice.

MATERIALS AND METHODS

Study Design, Population This single-center retrospective observational study was conducted at Fukuoka Universi-

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ty Hospital. Patients aged ≥18 years who had been prescribed amitriptyline between January and December 2022 were screened to identify those receiving established amitriptyline treatment before the supply restriction. Patients were eligible if they had received amitriptyline for at least 4 weeks and were receiving treatment when prescribing restrictions were implemented at our hospital in April 2023. Treatment discontinuation or switching was assessed during the observation period from April 2023 through March 2024. The study timeline is shown in Supplemental Fig. 1. Patients were excluded if they (1) transferred to another hospital or died during the observation period, (2) lacked necessary information in the medical records, or (3) received amitriptyline for indications other than pain management.

Data Collection Demographic and clinical data were collected from electronic medical records. The collected variables included sex, age, history of cancer, concomitant medications (opioids, non-opioid analgesics, and adjuvant analgesics), and prescribing department. Concomitant medication data were collected from the date of the last amitriptyline prescription. For patients with ongoing prescriptions, concomitant medication data from September 2023 were used. For patients who discontinued amitriptyline or switched to an alternative drug, the date of treatment modification was defined as the index date. The baseline NRS score was defined as the score recorded immediately before the index date, and the follow-up NRS score was the score recorded 8 weeks after treatment modification.

Endpoints The primary endpoint was the proportion of patients who discontinued amitriptyline or switched to another drug for any reason during the supply-restriction observation period. To quantify treatment disruption specifically documented as shortage-related, we additionally calculated the proportion of all eligible patients with documented shortage-related treatment modification. Additionally, among patients who underwent treatment modification, we calculated the proportion classified as documented shortage-related. Cases were classified as documented shortage-related if explicit documentation regarding the supply restriction, inability to continue amitriptyline, or shortage-related treatment modification was identified in the medical records. Treatment modifications attributed to inadequate pain control, adverse events, or both were categorized as attributable to other clinical reasons.

Exploratory analyses were performed among documented shortage-related cases with available baseline and 8-week NRS scores. First, the overall change in NRS scores from baseline to 8 weeks was evaluated using paired data from all eligible cases. Patients were then stratified according to the type of treatment modification: discontinuation of amitriptyline or switching to an alternative drug. Changes in NRS scores were evaluated separately in the discontinuation and switching groups. The change in NRS score was defined as the 8-week NRS score minus the baseline NRS score. To account for pain intensity before treatment modification, patients were descriptively stratified according to baseline NRS scores of ≤3, 4–6, and ≥7. These categories were based on the Japanese Society for Palliative Medicine guideline, which pragmatically classifies NRS scores of 1–3, 4–6, and 7–10 as mild, moderate, and severe pain, respectively, based on expert consensus; an NRS score of 0 was included in the lowest category. These categories were used solely for descriptive stratification.

To assess potential selection bias in the exploratory NRS analysis, documented shortage-related cases with paired baseline and 8-week NRS scores were compared with those without paired NRS scores. The characteristics compared were age, sex, history of malignancy, concomitant analgesic medications, and prescribing department.

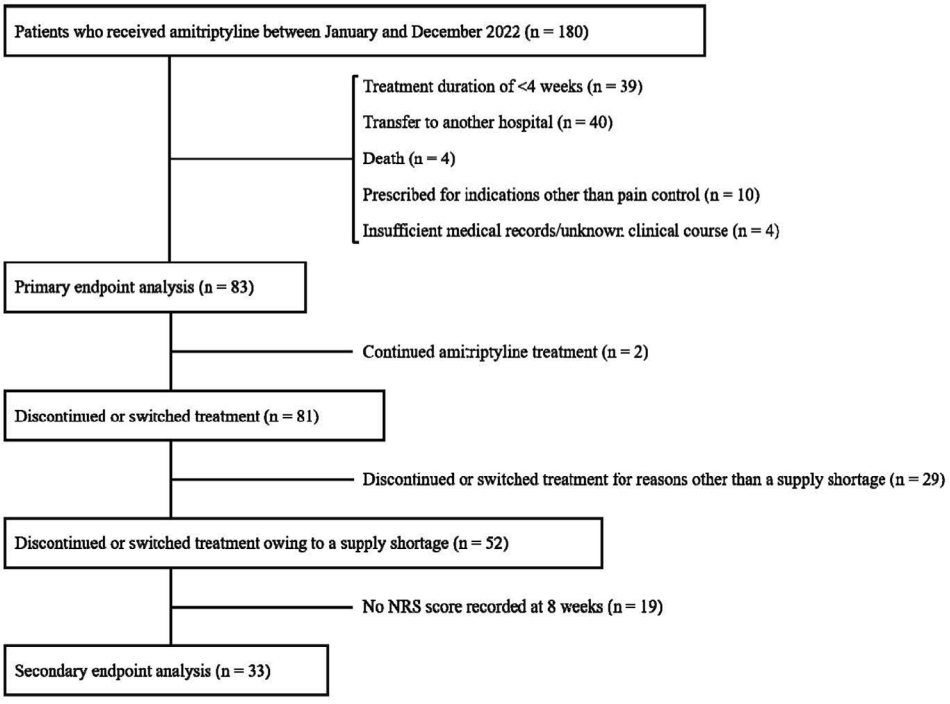

Fig. 1. Patient Selection Flowchart

Abbreviations: NRS, Numerical Rating Scale.

Statistical Analysis Continuous variables are presented as medians with interquartile ranges, and categorical variables as numbers and percentages. Paired NRS scores at baseline and 8 weeks were compared using the Wilcoxon signed-rank test. Changes in NRS scores, calculated as the 8-week score minus the baseline score, were compared between the discontinuation and switching groups using the Mann–Whitney U test. Changes in NRS scores according to the baseline NRS categories of ≤3, 4–6, and ≥7 were summarized descriptively and graphically for the overall cohort and the discontinuation and switching groups. Because of the small number of patients in each baseline NRS category, no formal statistical comparisons were performed between these strata. To assess potential selection bias, characteristics were compared between documented shortage-related cases with and without available paired NRS scores. Continuous variables were compared using the Mann–Whitney *U* test, and categorical variables were compared using Fisher's exact test. All statistical analyses were performed using EZR (Jichi Medical University, Tochigi, Japan), a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria).[7] Specifically, a modified version of R Commander that includes statistical functions frequently used in biostatistics was used.

Ethical Considerations This study was approved by the Medical Ethics Review Board of Fukuoka University (approval number: H25-01-005) and conducted in compliance with the ethical standards of the institution for research involving human participants and the Declaration of Helsinki. Informed consent was not required from the participants because of the retrospective nature of this study.

RESULTS

Patients Of 180 patients identified during the screening period, 97 met the exclusion criteria. Consequently, 83 patients receiving amitriptyline treatment when prescribing restrictions were implemented were included in the analysis (Fig. 1). The baseline characteristics of the study population are presented in Table 1. The median age of the patients was 60 years and 15 (18.1%) had a history of cancer. Anesthesiology was the most common prescribing department, accounting for 60 patients (72.3%). Regarding concomitant analgesics prescribed on the date of the last amitriptyline prescription, opioids were co-administered in 30 patients (36.1%).

Amitriptyline Treatment Modification and Documented Reasons During the supply-restriction observation period, 81 of the 83 patients (97.6%) discontinued amitriptyline or switched to another drug for any reason. Of these patients, 44 discontinued amitriptyline and 37 switched to another drug.

Of the 83 patients included in the primary analysis, 52 (62.7%) had treatment modifications explicitly documented as shortage-related. These patients accounted for 64.2% of the 81 patients who underwent treatment modification. The remaining 29 patients (35.8% of those with treatment modification) underwent treatment modification for other clinical reasons, including inadequate pain control, adverse events, or both (Fig. 2).

Among the 52 documented shortage-related cases, 22 discontinued amitriptyline and 30 switched to an alternative drug. Duloxetine was the most frequently selected alternative medication, used in 19 patients. Two patients received two alternative medications: duloxetine plus nonsteroidal anti-inflammatory drugs in one patient and vortioxetine plus naratriptan in another (Table 2).

Exploratory Analysis of Changes in NRS Scores Among the 52 documented shortage-related cases, paired baseline and 8-week NRS scores were available for 33 patients. To assess potential selection bias, the 33 patients with paired NRS scores were compared with the 19 patients without paired NRS

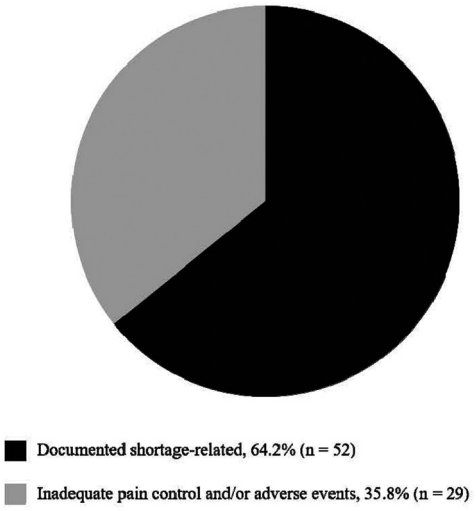

Fig. 2. Classification of Documented Reasons for Amitriptyline Discontinuation or Switching among Patients Who Underwent Treatment Modification (n = 81)

Table 1. Baseline Patient Characteristics of the Study Population

Variable	n = 83
Age, years	60 [49, 71]
Female sex	50 (60.2)
History of malignancy	15 (18.1)
Concomitant medications	
Opioids	30 (36.1)
NSAIDs/Acetaminophen	19 (22.9)
Adjuvant analgesics	58 (69.9)
Department	
Anesthesiology	60 (72.3)
Neurology	16 (19.3)
Other	7 (8.4)

Data are presented as n (%) or median [interquartile range]
Abbreviations: NSAIDs, nonsteroidal anti-inflammatory drugs.

Table 2. Alternative Medications Used in Documented Shortage-Related Switching Cases

Alternative medication	n = 30 (counts are not mutually exclusive)
Duloxetine	19
Vortioxetine	4
NSAIDs/Acetaminophen	2
Clomipramine	3
Sertraline	2
Naratriptan	1
Eperisone	1

Abbreviations: NSAIDs, nonsteroidal anti-inflammatory drugs

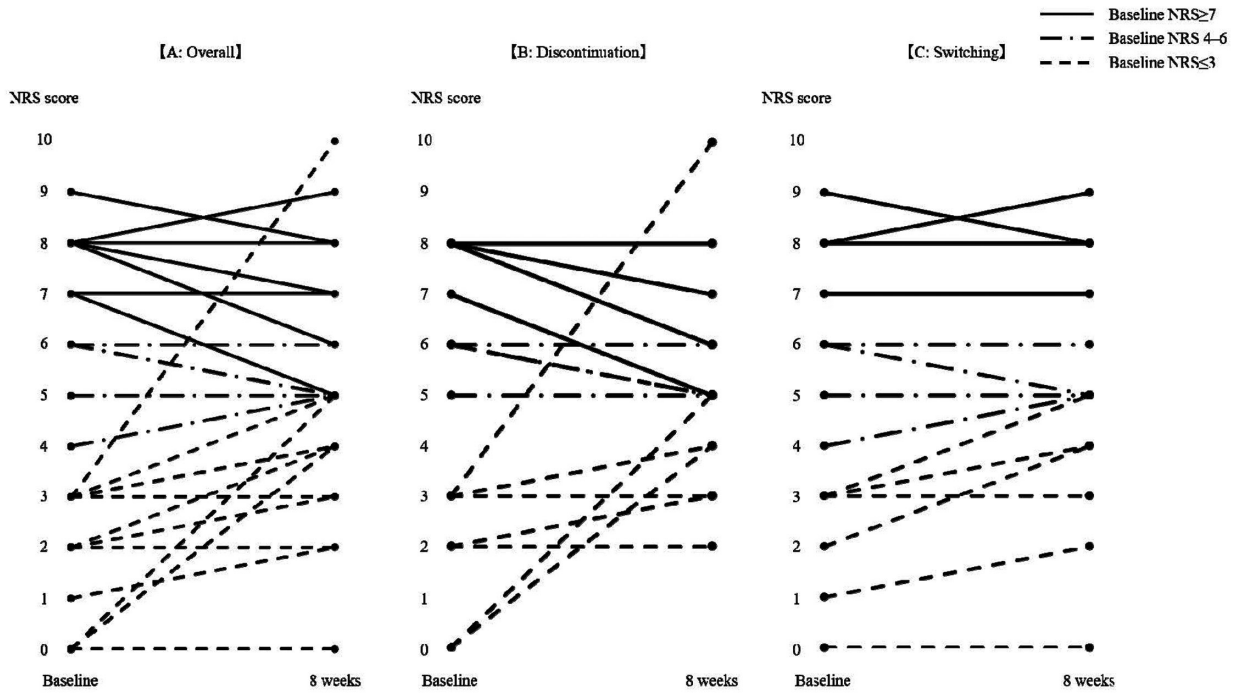

Fig. 3. Changes in NRS Scores from Baseline to 8 Weeks According to Treatment Modification and Baseline NRS Category

Individual changes in NRS scores are shown for (A) all patients with available paired NRS scores (n = 33), (B) patients who discontinued amitriptyline (n = 17), and (C) patients who switched to an alternative drug (n = 16). Patients were descriptively stratified according to baseline NRS score categories of ≤3, 4–6, and ≥7. Each line represents an individual patient and connects the baseline NRS score to the score recorded 8 weeks after treatment modification. Abbreviation: NRS, Numerical Rating Scale.

scores. No statistically significant differences were observed in age, sex, history of malignancy, or concomitant analgesic medications. However, the distribution of prescribing departments differed significantly between groups ($p < 0.001$). All 33 patients with available paired NRS scores were treated in the Department of Anesthesiology, whereas the group without available paired NRS scores included patients from Anesthesiology, Neurology, and other departments (Supplemental Table 1).

The median NRS score was 5 [interquartile range (IQR), 3–7] at baseline and 5 [IQR, 4–6] at 8 weeks, with a median change of 0 [IQR, 0–1]. No statistically significant overall change was observed ($p = 0.21$). NRS scores increased in 11 patients, remained unchanged in 15 patients, and decreased in 7 patients.

When patients were descriptively stratified according to baseline NRS score, 15 patients had scores ≤3, 9 had scores of 4–6, and 9 had scores ≥7. NRS scores increased in 9 of 15 patients (60.0%) with baseline scores ≤3, 1 of 9 patients (11.1%) with baseline scores of 4–6, and 1 of 9 patients (11.1%) with baseline scores ≥7.

Of the 33 patients, 17 discontinued amitriptyline and 16 switched to an alternative drug. In the discontinuation group, the median NRS score was 5 [IQR, 3–6] at baseline and 5 [IQR, 4–6] at 8 weeks, with a median change of 0 [IQR, −1 to 1]. In the switching group, the corresponding values were 5 [IQR, 3–7], 5 [IQR, 4–7], and 0 [IQR, 0–1], respectively. The change in NRS scores did not differ significantly between the groups ($p = 0.48$). In both treatment-modification groups, increases in NRS scores occurred mainly among patients with baseline scores ≤3 and were less frequent among those with higher baseline scores. Individual NRS trajectories according to treatment modification and baseline NRS category are shown in Fig. 3.

DISCUSSION

In this study, 52 of the 83 eligible patients (62.7%) had amitriptyline treatment modifications explicitly documented as shortage-related. Overall, 81 patients (97.6%) discontinued amitriptyline or switched to another drug for any reason during the observation period. However, the overall treatment-modification rate should not be attributed entirely to the supply shortage, because 29 patients underwent treatment modification because of inadequate pain control and/or adverse events.

This finding is consistent with previous reports describing treatment disruption and increased healthcare burden associated with drug shortages.[5, 8] To our knowledge, few studies in Japan have specifically evaluated the clinical consequences of drug shortages in patients receiving pharmacotherapy for chronic pain. Because amitriptyline has a unique role in the management of neuropathic pain in Japan, supply instability may have disproportionately affected treatment continuity in this population.

An analysis of the French pharmacovigilance database demonstrated a marked increase in adverse event reports related to drug shortages between 2004 and 2019, with insufficient effectiveness of alternative treatments being frequently reported.[9] In the present study, amitriptyline treatment was maintained in only two patients, suggesting that treatment continuation was considered necessary in selected cases despite the supply restriction.

Among patients with available paired NRS scores, no sta-

tistically significant change was observed from baseline to 8 weeks after treatment modification. When patients were stratified according to the type of treatment modification, the change in NRS scores did not differ significantly between the discontinuation and switching groups. Nevertheless, individual NRS trajectories varied within both groups.

When patients were descriptively stratified according to baseline NRS scores, NRS scores increased in 9 of 15 patients (60.0%) with baseline scores ≤3, compared with 1 of 9 patients (11.1%) in each of the 4–6 and ≥7 categories. This pattern may indicate the loss of previously maintained pain control in some patients after treatment modification. The trajectories observed among patients with higher baseline scores may have reflected reassessment and optimization of pain management following treatment modification, although the specific clinical processes underlying these changes were not systematically evaluated. These findings suggest that changes in pain scores should be interpreted in the context of pain intensity before treatment modification. Accordingly, comparisons between the discontinuation and switching groups should be regarded as exploratory because treatment strategies reflected clinical decision-making rather than random assignment. However, the absence of a statistically significant difference between the discontinuation and switching groups should not be interpreted as evidence of equivalence between the two treatment strategies. The selection of treatment discontinuation or switching was not randomized and may have been influenced by clinical factors that were not fully captured in the medical records. In addition, the small number of patients in each treatment-modification group and baseline NRS category precluded definitive conclusions. Because all patients included in the NRS analysis were treated in the Department of Anesthesiology, these exploratory findings may not be representative of all documented shortage-related cases.

Duloxetine was the most frequently selected alternative medication in this study. This finding is consistent with current Japanese guidelines recommending duloxetine as a first-line treatment option for neuropathic pain.[6] However, alternative medication selection varied among patients, and the effectiveness of individual switching strategies could not be determined in this study. Further studies are needed to evaluate the clinical outcomes of specific therapeutic alternatives used during pharmaceutical shortages.

The present findings also highlight the broader challenges associated with pharmaceutical supply instability. In recent years, repeated shipment restrictions and supply adjustments involving generic drugs have occurred in Japan, prompting temporary policy measures by the Ministry of Health, Labour and Welfare. These circumstances illustrate the challenges of maintaining stable pharmacotherapy during periods of supply disruption. Drug shortages have also become an international policy issue. In the European Union, the need for earlier detection systems and coordinated responses across countries has been emphasized.[10] These circumstances suggest that pharmaceutical shortages are not only local supply problems but also global supply chain challenges that require international cooperation and coordinated management strategies. These findings also highlight the importance of proactive shortage management strategies, including early communication between physicians and pharmacists and careful planning of therapeutic alternatives for vulnerable patient populations.

This study has several limitations. First, this was a retrospective single-center study, which may limit the generalizability of the findings. Second, pain outcomes were assessed primarily using NRS scores, whereas other clinically relevant outcomes were not systematically evaluated. In addition, analyses stratified according to baseline NRS scores were descriptive, and the observed changes may have been influenced by floor and ceiling effects, regression to the mean, and the absence of consideration of the minimal clinically important difference. Third, because of the retrospective observational design and the lack of an appropriate comparator group, causal relationships between pharmaceutical shortages and changes in pain control could not be established. Patients were not randomly assigned to treatment discontinuation or switching, and the clinical factors underlying the choice of treatment modification were not fully evaluated. Consequently, confounding by indication may have affected the comparison between the discontinuation and switching groups. The small sample size in each treatment-modification group and baseline NRS category further limited the precision and statistical power of the exploratory analyses. Finally, classification of shortage-related cases depended on medical record documentation, and paired NRS scores were available for only 33 of the 52 documented shortage-related cases. All patients included in the NRS analysis were treated in the Department of Anesthesiology, whereas the group without paired NRS scores included patients from several departments. This imbalance indicates potential selection bias and limits the generalizability of the exploratory NRS findings to the entire shortage-related cohort.

During the supply-restriction observation period, most patients discontinued amitriptyline or switched to another drug, and approximately two-thirds of these treatment modifications were explicitly documented as shortage-related. Pain outcomes after treatment modification were heterogeneous. These findings demonstrate the substantial treatment disruption associated with the supply shortage and highlight the importance of stable medication supply systems.

Acknowledgments We would like to thank Editage (www.editage.jp) for English language editing.

Competing interests The authors declare no competing interests.

Funding No funding was received for this study.

Authors' contributions HS, MU, and SaK designed the study, collected and analyzed the data, and drafted the manuscript. MT, TY, TN, KM, HK, and SuK critically revised the manuscript. All the authors have read and approved the final version of the manuscript.

Availability of data and materials Not applicable.

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