BPB Reports

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# Analysis of Drug-Induced Xerostomia using the Japanese Adverse Drug Event Report Database

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Received September 3, 2025; Accepted October 7, 2025

**Xerostomia is a condition characterized by the primary complaint of dry mouth, which can lead not only to oral issues but also to systemic diseases and a decline in quality of life (QOL). While drug adverse reactions are among its causes, the underlying mechanisms and risks associated with each medication remain unclear. Therefore, this study aimed to clarify aspects of drug-induced xerostomia using the Japanese Adverse Drug Event Report Database. Five Preferred Terms defined by the Japanese version of the Medical Dictionary for Regulatory Activities, including Thirst, Dry mouth, Dry throat, Lip dry, and Salivary hyposecretion, were classified as representing adverse reactions related to xerostomia and were extracted. An analysis of approximately 20 years of data revealed 781 cases were reported as xerostomia. Signals were detected for 27 drugs, classified into 10 categories according to the Anatomical Therapeutic Chemical classification. Of these, 20 drugs had xerostomia descriptions in their package inserts, and 12 drugs were assigned scores on the Anticholinergic Risk Scale. Signals were also detected for drugs not widely known to be associated with xerostomia, such as ANTINEOPLASTIC AGENTS and VACCINES, suggesting the influence of patients' underlying diseases and concomitant medications. Both the newly identified seven drugs and those that do not exhibit anticholinergic effects should be evaluated in conjunction with further clinical data. Future investigations considering patients' underlying conditions and concomitant medications are important. Furthermore, since xerostomia may impact QOL and systemic health, pharmacists are expected to play an active role in its prevention and early detection.**

**Key words** drug safety information, thirst, dry mouth, dry throat, lip dry, salivary hyposecretion

## INTRODUCTION

Xerostomia is defined as a subjective sensation of dry mouth, often accompanied by reduced salivary secretion, which plays a crucial role in maintaining oral homeostasis.[1,2] In 2022, a new classification for xerostomia was announced by four academic societies in Japan, which defines xerostomia not only as an objective finding of reduced salivary secretion but also as a subjective sensation of dry mouth. Xerostomia affects 19.1% of older individuals according to self-reported data.[3] It can lead to local complications such as dental caries, periodontal disease, oral mucosal pain, glossodynia, taste disorders, and dysphagia.[4,5] Additionally, xerostomia may also increase the risk of systemic conditions, including frailty, sarcopenia, malnutrition, and cognitive decline, through decreased appetite, social isolation, and reduced quality of life (QOL).[5-10] Xerostomia has multifactorial causes, including salivary gland diseases, systemic conditions such as diabetes and depression, radiation therapy for head and neck cancer, drug adverse reactions, and stress.[11,12] Among these, drug-induced xerostomia is common.[13] Various drugs such as anticholinergics and antidepressants, have been reported to suppress salivary secretion and induce xerostomia.[5] In particular, the occurrence of xerostomia may increase with the number of drugs taken by older individuals.[14] Our previous research revealed that approximately 80% of elderly patients visiting hospitals are taking at least one xerostomia-inducing drug.[15] However, the occurrence of drug-induced xerostomia is often unclear. While it is recognized in clinical practice, there are still no reports based on database analyses or other concrete evidence.

Large-scale spontaneous reporting databases have been established in many countries to enable pharmacovigilance through the early identification and monitoring of drug-related adverse reactions.[16] In Japan, the Pharmaceuticals and Medical Devices Agency (PMDA) has collected reports of adverse reactions related to both prescription and over-the-counter drugs since 2004.[17] The JADER database is openly accessible to the public, with all personal information being fully anonymized. This database has been increasingly utilized for studies to detect drug signals in pharmaceuticals by statisti-

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cal methods. Disproportionality analyses are often conducted using frequentist approaches, with the Reporting Odds Ratio (ROR) and Proportional Reporting Ratio (PRR) being among the most widely applied metrics. However, no comprehensive analyses have yet been conducted specifically on xerostomia. Therefore, this study aimed to investigate the reporting patterns of xerostomia and identify the signals for drug-induced xerostomia, using the JADER database. The analysis of signal patterns for xerostomia in this study is crucial for identifying drugs that may cause dry mouth, excluding those with anticholinergic effects. This contributes to clinical risk assessment and awareness, as xerostomia is an adverse reaction associated with reduced QOL and systemic conditions.

## MATERIALS AND METHODS

**Construction of the Analytical Data Table** The JADER database was downloaded from the PMDA website (https://www.pmda.go.jp/safety/info-services/drugs/adr-info/suspected-adr/0003.html). We downloaded the JADER data available to the public as of May 2025 (accessed on May 12, 2025). All reports published between April 2004 and January 2025 were included in this analysis. Since this study specifically focused on adverse reactions, we only utilized the drug information and adverse events tables. For this study, only the records of suspected drugs were extracted in order to evaluate a strong association between the drugs and adverse reactions. Before linking the datasets by ID number, duplicate cases were identified and excluded, as the same case could appear multiple times with differing prescription or event onset dates. When multiple suspected drugs were reported in a single report, each was considered as an independent adverse reaction.

**Signal Detection** We extracted specific adverse events using Preferred Terms (PTs) recommended for JADER analysis from version 28.0 of the Japanese Medical Dictionary for Regulatory Activities (MedDRA/J), with consideration of timeliness.[18] The following five PTs (PT Codes) were set as the specific adverse events in this study: “Dry mouth (10013781),” “Thirst (10043458),” “Dry throat (10013789),” “Lip dry (10024552),” and “Salivary hyposecretion (10039425).” Any reports that included these terms as recorded adverse events were extracted for analysis. Three pharmacovigilance indices were utilized to detect signals: ROR, PRR, and the Chi-squared statistics ($\chi^2$). The criteria for signal detection were as follows: (a) ROR: the lower bound of the 95% confidence interval (CI) >1, (b) PRR ≥2, $\chi^2$ ≥4, and number of specific cases ≥3.[19-21] All dataset processing and analyses were performed using R Analytic Flow 3.3.1 (Ef-Prime, Inc., Tokyo, Japan; https://r.analyticflow.com/en/download/).

**Drug Classification** The candidates for xerostomia-inducing drugs that met the signal criteria were classified using the Anatomical Therapeutic Chemical (ATC) Classification published by the Norwegian Institute of Public Health (https://atcddd.fhi.no/atc_ddd_index/). Furthermore, the signal-detected drugs were confirmed for descriptions of dry mouth as an adverse reaction in the package inserts of the drugs. Additionally, we examined whether these drugs correspond to the Japanese Anticholinergic Risk Scale 2nd edition published by Japanese Society of Geriatric Pharmacy.[22]

## RESULTS

**Number of Adverse Event Reports and Signal Detection** The cases investigated were reported between April 2004 and January 2025, totaling 965,285 cases. Upon reviewing the analysis table, out of 2,516,004 adverse events, 781 were reported as xerostomia-related events. The number of reports for "Dry mouth" was 192, and 121 drugs were reported as suspected drugs. There were six drugs that met the criteria (Table 1). Notably, solifenacin succinate, and fesoterodine fumarate showed high ROR values of 62.4 and 62.1, respectively. The number of reports for "Thirst" was 530, and 236 drugs were reported as suspected drugs. A relatively large number of drugs showed signals, with 24 drugs being identified (Table 2). Fesoterodine fumarate also showed the highest ROR value of 60.4 for thirst among the 24 drugs. The number of reports for "Dry throat" was 19, and 11 drugs were reported as suspected drugs. Only the SARS-CoV-2 RNA vaccine showed a signal (ROR value of 15.7), and the total number of adverse event reports for this drug was 111,160 (Table 3). On the other hand, no drugs were identified with signals for "Lip dry" or "Salivary hyposecretion."

**Classification of Signal-Detected Drugs with Reference to Anticholinergic Risk Scale and Package Inserts** The results of categorizing the 27 drugs that had signal detection for any of the adverse events "Dry mouth," "Thirst," or "Dry throat" by therapeutic classification are shown in Table 4. PSYCHOANALEPTICS (7 drugs) were the most common, followed by PSYCHOLEPTICS (4 drugs), and ANTINEOPLASTIC AGENTS (4 drugs). Among these drugs, 12 were assigned scores on the Japanese Anticholinergic Risk Scale 2nd Edition. Specifically, six drugs were categorized as score 1, three drugs as score 2, and three drugs as score 3. The details of the scores for these 12 drugs, with ratings of 1, 2, and 3 indicated in parentheses, are presented in Table 4. All UROLOGICALS identified through signal detection were assigned the maximum score of 3 on the risk scale.

Furthermore, among the 27 drugs with signal detection, 20 drugs had descriptions in their package inserts indicating the potential for xerostomia as an adverse reaction. Among these 20 drugs, the following six had particularly high reported inci-

**Table 1.** Statistical Measures of ROR and PRR for Dry Mouth.

| Drug name | ROR (95% CI) | $\chi^2$ | PRR | Case | Total |
|---|---|---|---|---|---|
| Solifenacin succinate | 62.4 (27.6 - 140) | 292.8 | 62.1 | 6 | 1,306 |
| Fesoterodine fumarate | 62.1 (31.8 - 121) | 457.2 | 61.9 | 9 | 1,999 |
| Bivalent human papillomavirus-like particle vaccine | 11.0 (5.19 - 23.5) | 52.27 | 11.0 | 7 | 8,593 |
| Cetuximab | 10.2 (4.18 – 24.7) | 31.78 | 10.2 | 5 | 6,602 |
| Paroxetine hydrochloride hydrate | 5.67 (1.81 – 17.7) | 7.209 | 5.67 | 3 | 7,029 |
| Pemetrexed disodium hydrate | 4.79 (1.53 – 4.79) | 5.505 | 4.79 | 3 | 8,313 |

**Table 2.** Statistical Measures of ROR and PRR for Thirst.

| Drug name | ROR (95% CI) | $\chi^2$ | PRR | Case | Total |
|---|---|---|---|---|---|
| Fesoterodine fumarate | 60.4 (40.0 – 91.1) | 1266 | 59.7 | 24 | 1,999 |
| Clotiazepam | 18.1 (6.77 – 48.6) | 48.22 | 18.1 | 4 | 1,058 |
| Escitalopram oxalate | 12.7 (4.74 – 34.0) | 31.88 | 12.7 | 4 | 1,509 |
| Losartan potassium/ hydrochlorothiazide combination | 12.6 (4.03 – 39.1) | 21.21 | 12.5 | 3 | 1,143 |
| Venlafaxine hydrochloride | 12.3 (5.85 – 26.0) | 61.04 | 12.3 | 7 | 2,733 |
| Methylphenidate hydrochloride | 11.0 (4.11 – 29.5) | 26.79 | 11.0 | 4 | 1,741 |
| Amoxapine | 11.0 (3.54 – 34.3) | 18.09 | 11.0 | 3 | 1,301 |
| Solifenacin succinate | 11.0 (3.53 – 34.2) | 18.01 | 11.0 | 3 | 1,306 |
| Bazedoxifene acetate | 11.0 (3.53 – 34.3) | 18.04 | 11.0 | 3 | 1,304 |
| Tolvaptan | 10.2 (5.47 – 19.2) | 72.80 | 10.2 | 10 | 4,726 |
| Paroxetine hydrochloride hydrate | 9.70 (5.70 – 16.5) | 97.86 | 9.68 | 14 | 7,029 |
| Sertraline hydrochloride | 8.22 (3.40 – 19.8) | 24.60 | 8.21 | 5 | 2,917 |
| Blonanserin | 7.92 (2.54 – 24.7) | 11.79 | 7.91 | 3 | 1,809 |
| Spironolactone | 5.71 (2.36 – 13.8) | 14.82 | 5.70 | 5 | 4,197 |
| Ipragliflozin L-proline | 5.40 (1.74 – 16.8) | 6.763 | 5.40 | 3 | 2,650 |
| Nintedanib ethanesulfonate | 5.32 (1.71 – 16.6) | 6.597 | 5.31 | 3 | 2,692 |
| Mirtazapine | 5.23 (1.68 – 16.3) | 6.429 | 5.23 | 3 | 2,736 |
| Olanzapine | 4.96 (2.22 – 11.1) | 15.02 | 4.96 | 6 | 5,799 |
| Quetiapine fumarate | 4.10 (1.70 – 9.89) | 8.726 | 4.10 | 5 | 5,835 |
| Furosemide | 3.90 (1.74 – 8.72) | 10.07 | 3.90 | 6 | 7,369 |
| Pregabalin | 3.77 (2.07 – 6.85) | 19.27 | 3.77 | 11 | 14,073 |
| Acetaminophen | 2.95 (1.23 – 7.14) | 4.615 | 2.96 | 5 | 8,080 |
| SARS-CoV-2 RNA vaccine | 2.87 (2.20 – 3.74) | 64.82 | 2.87 | 62 | 111,160 |
| Ipilimumab | 2.38 (1.42 – 3.97) | 10.31 | 2.38 | 15 | 30,458 |

**Table 3.** Statistical Measures of ROR and PRR for Dry Throat.

| Drug name | ROR (95% CI) | $\chi^2$ | PRR | Case | Total |
|---|---|---|---|---|---|
| SARS-CoV-2 RNA vaccine | 15.7 (6.33 – 39.1) | 55.29 | 15.7 | 8 | 111,160 |

**Table 4.** Number of Adverse Event Reports by Anatomical Therapeutic Chemical Classification

| Classification | Drugs (Anticholinergic Risk Scale Score) | The number of drugs |
|---|---|---|
| N06 PSYCHOANALEPTICS | Amoxapine (3), Paroxetine hydrochloride hydrate (2), Mirtazapine (1), Escitalopram oxalate (1), Sertraline hydrochloride (1),Venlafaxine hydrochloride (1), Methylphenidate Hydrochloride | 7 |
| N05 PSYCHOLEPTICS | Clotiazepam, Olanzapine (2), Quetiapine fumarate (2), Blonanserin (1) | 4 |
| L01 ANTINEOPLASTIC AGENTS | Nintedanib ethanesulfonate, Pemetrexed disodium hydrate, Ipilimumab, Cetuximab | 4 |
| C03 DIURETICS | Spironolactone, Tolvaptan, Furosemide (1) | 3 |
| N02 ANALGESICS | Acetaminophen, Pregabalin | 2 |
| G04 UROLOGICALS | Solifenacin succinate (3), Fesoterodine fumarate (3) | 2 |
| J07 VACCINES | SARS-CoV-2 RNA vaccine,Bivalent human papillomavirus-like particle vaccine | 2 |
| C09 AGENTS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM | Losartan potassium/ hydrochlorothiazide combination | 1 |
| A10 DRUGS USED IN DIABETES | Ipragliflozin L-proline | 1 |
| G03 SEX HORMONES AND MODULATORS OF THE GENITAL SYSTEM | Bazedoxifene acetate | 1 |

dence rates (≥10%) of xerostomia: tolvaptan (Thirst, 56.8%), fesoterodine fumarate (Dry mouth, 36.5%), solifenacin succinate (Dry mouth, 28.3%), venlafaxine hydrochloride (Dry mouth, 24.3%), mirtazapine (Thirst, 20.6%), and amoxapine (Thirst, 16.04%). In contrast, the following drugs had no mention of xerostomia-related adverse reactions in their package inserts: acetaminophen, nintedanib ethanesulfonate, pemetrexed disodium hydrate, ipilimumab, cetuximab, SARS-CoV-2 RNA vaccine, and Bivalent human papillomavirus-like particle vaccine.

## DISCUSSION

The purpose of this study was to clarify the reporting patterns of drug-induced xerostomia using the JADER database. We focused on five PTs representing xerostomia symptoms based on MedDRA/J for signal detection. As a result, we identified 27 drugs that could potentially induce xerostomia, including dry mouth, thirst, and dry throat. In terms of ATC classification, PSYCHOANALEPTICS were prominent. We newly identified that 7 out of 27 drugs did not have package inserts indicating the potential adverse reaction of xerostomia.

Among the drugs detected as signals in this study, PSY-

CHOANALEPTICS, PSYCHOLEPTICS, and UROLOGICALS primarily correspond to anticholinergics, which block muscarinic receptors on salivary glands and suppress saliva secretion, leading to dry mouth symptoms.[23] Schoppmeier *et al*. reported a correlation between increased cumulative exposure to these drugs and the manifestation of dry mouth symptoms, as well as reduced saliva secretion.[24] Our study also suggested an association between the intake of anticholinergic drugs and dry mouth symptoms. Furthermore, the Japanese Anticholinergic Risk Scale 2nd edition, developed by the Japanese Society of Geriatric Pharmacology, aims to evaluate the risks of anticholinergic drugs frequently used in the elderly to avoid drug-related adverse events. It assigns scores from 1 to 3 to 158 drugs for individual risk assessment and overall anticholinergic burden evaluation.[22] In our study, 12 out of the 27 signal-detected drugs were scored, indicating a relationship between the Anticholinergic Risk Scale and dry mouth symptoms. Additionally, in this study, signals were detected for three diuretics. Furthermore, the combination drug of losartan potassium and hydrochlorothiazide, which is an antihypertensive agent, also includes hydrochlorothiazide, a type of diuretic. Diuretics increase urine output by inhibiting the reabsorption of $Na^+$, but they can also induce dry mouth symptoms by increasing plasma osmolality and stimulating the thirst center in the hypothalamus due to the reduction in body fluid volume.[25,26] On the other hand, although the underlying diseases of the patients were not analyzed in this study, they might influence the manifestation of symptoms. For example, the association between diabetes and dry mouth symptoms has been previously noted, with reports indicating reduced saliva secretion in diabetic patients compared to non-diabetic individuals.[27,28] In diabetic patients, dry mouth symptoms could potentially be induced by factors such as damage to the salivary gland parenchyma, neuropathy, polyuria, and dehydration.[11] Among the signal-detected drugs, Ipragliflozin L-Proline is classified as an antidiabetic agent, suggesting that the reported adverse event of dry mouth symptoms might have been attributable to the underlying condition of diabetes in the patients.

Furthermore, signal detection was observed for the ANTINEOPLASTIC AGENTS, nintedanib, pemetrexed, ipilimumab, and cetuximab. However, xerostomia is not listed as known adverse reactions in the package inserts for these drugs. These drugs have been reported to potentially affect salivary gland function not only by exerting direct cytotoxic impacts but also by increasing reactive oxygen species and inducing inflammation. In particular, immune checkpoint inhibitors have been associated with salivary gland impairment through the elevation of inflammatory cytokines such as IFN-γ and IL-6.[29] On the other hand, gastrointestinal symptoms such as vomiting, diarrhea, and stomatitis are documented, which could lead to changes in eating and drinking habits, resulting in dehydration and subsequently causing xerostomia. Additionally, these drugs are commonly co-administered with antihistamines, antipyretic analgesics, and systemic steroids to prevent infusion reactions and other adverse reactions.[30] Since the concomitant medications in each case were not analyzed in this study, it is also necessary to consider the possibility that these supportive therapy drugs might induce dry mouth symptoms. In this study, the COVID-19 vaccine was identified as a signal-detected drug for the two "Thirst" and "Dry throat," with 70 adverse event reports, the highest among all drugs analyzed. Regarding the COVID-19 vaccine, it has been suggested that the antigenic spike protein generated following vaccination may be involved in salivary secretion dysfunction.[31] However, according to Yamaoka *et al*., adverse event reports related to COVID-19 vaccines account for about 5% of the entire JADER database, which is said to influence the increase in ROR and PRR.[32] Therefore, considering that this study includes reports from 2021 onward, following the approval of COVID-19 vaccines in Japan, it is necessary to consider the potential impact of the surge in COVID-19 vaccine-related reports on signal detection. Specifically, some of the signal detected drugs may have been influenced by concomitant medications administered during COVID-19 vaccines. In this study, the use of concomitant drugs for adverse reactions to the vaccine was also not included, as individual patients cannot be uniquely identified across reports in the JADER database. Furthermore, the COVID-19 pandemic may have increased overall reporting frequency by raising awareness among reporters including healthcare professionals. To assess the concordance between the detected signals and clinical evidence, we compared them with the information provided in the package inserts. Of the drugs with detected signals, 74% (20 out of 27 drugs) had package inserts indicating the potential adverse reactions of xerostomia. Specifically, some drugs such as tolvaptan and fesoterodine fumarate showed a very high incidence rate, supporting the validity of the signal detection. Additionally, seven new drugs have been identified as potentially causing xerostomia in this study. However, since the number of reports for these seven drugs was relatively small, caution is warranted in interpreting these results due to potential limitations in statistical validity. This study has several limitations. First, spontaneous reporting is inherently affected by reporting biases, including underreporting, selective reporting influenced by media attention or safety alerts. Second, the analysis may be influenced by confounding factors such as concomitant drug use and underlying diseases, which cannot be fully considered in the JADER database. Further analysis of database data is expected to support these findings, and this work is currently ongoing.

**Conclusion** This study revealed that there are associations between xerostomia and drugs including PSYCHOANALEPTICS and PSYCHOLEPTICS. While anticholinergic drugs are a major mechanism of drug-induced xerostomia, we also identified new drugs that are not listed on the Anticholinergic Risk Scale. Furthermore, signals were also detected for drugs such as ANTINEOPLASTIC AGENTS and VACCINES, which are not widely recognized as being associated with xerostomia. This highlights the need for multifaceted investigations that consider patients' underlying conditions and concomitant medications. Since xerostomia can affect patients' quality of life and systemic health, it is essential to assess the risk when prescribing medications known to induce dry mouth. Pharmacists should play an active role in the prevention and early detection of drug-induced xerostomia.

**Acknowledgments** We are grateful to Dr. Yuta Yokoyama from Keio University for providing valuable comments on the use of MedDRA/J.

**Funding** This study was supported by JSPS KAKENHI (Grant Number: 25K10112). The funding source had no role in the preparation of the data or manuscript.

**Conflict of interest** The authors declare no conflict of interest.

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