

## Executive Summary

Health Labor Research Grant from the Ministry of Health, Labor, and Welfare, Research on Pharmaceutical and Medical Regulatory Science, Research Report 2024

**Research on substance designation of pharmaceuticals suspected to be abused (24KC2005)**

**Aims:** It is an urgent task to consider revising the scope of designated ingredients for " pharmaceuticals suspected to be abused " The purpose of this study was to grasp the actual situation of abuse and dependence on over-the-counter drugs at specialized addiction medical institutions to collect and organize information on the addictive properties of each ingredient and the psychoactive properties that lead to abuse, and to create a draft opinion on the scope of designation for " pharmaceuticals suspected to be abused " The conclusions of each study are as follows:

**Study 1:** According to a nationwide survey of patients visiting addiction specialist medical institutions, it was revealed that the over-the-counter drugs that were mainly abused in over-the-counter drug cases from April to May 2024 contained not only ingredients designated as " pharmaceuticals suspected to be abused " but also undesignated ingredients such as dextromethorphan, diphenhydramine, allylisopropylacetylurea, and caffeine. The average age of patients was 29.1 years old, 71.4% were female, and the main trigger for the initiation of abuse was family and friendship relationships. The main effects expected from abuse were improvement of depression, relaxation/calmness, mood improvement/tension, floating/floating feeling, and euphoria. Approximately 20% of cases involved emergency transport episodes involving hospitalization.

**Study 1 Appendix:** According to a content analysis of inquiries regarding the intentional ingestion of over-the-counter drugs, the number of inquiries has been increasing from 2019 to 2023, and the patients are mostly female and younger. The over-the-counter drugs that are the subject of intentional ingestion were often caffeine-containing anti-drowsiness drugs,

diphenhydramine-containing allergy drugs, diphenhydramine-containing hypnotic sedatives, and dextromethorphan-containing cough suppressants and expectorants, in addition to products designated as " pharmaceuticals suspected to be abused "

Study 2: According to a literature survey conducted through academic literature search sites such as PubMed, the health effects of dextromethorphan overdose were reported to be mild intoxication, excitement, and dissociative states at 1.5-2.5 mg/kg, euphoria, hallucinations, and impaired coordination at 2.5-7.5 mg/kg, and hallucinations, memory disorders, violent behavior, and death due to cardiac and respiratory arrest at 15 mg/kg or more. The health effects of diphenhydramine overdose were reported to be hypertension and tachycardia at 7.5-7.7 mg/kg, excitement, irritability, confusion, hallucinations, delusions, respiratory depression, and coma at 8.3-19.8 mg/kg, and nystagmus and fainting at 35.6-61.1 mg/kg. Ingestion of large amounts of caffeine or rapid reduction or cessation of continuous caffeine use can cause withdrawal symptoms such as discomfort, irritability, restlessness, craving, mild body pain, migraine, drowsiness, insomnia, fatigue, lethargy, and feelings of self-harm. Allylisopropylacetylurea is not used internationally as a medicine, and almost no information has been reported on its health effects.

Study 3: According to a study using social networking services as a source of information, 15 types of over-the-counter drug products were extracted by analyzing posts including "OD reports" posted on X (formerly Twitter) from April 18 to May 29, 2024. Of these, 14 types of products contained dextromethorphan, diphenhydramine, allylisopropylacetylurea, and caffeine, rather than designated ingredients of pharmaceuticals that may be abused. Through content analysis of the posts, it was suggested that euphoria, dissociative symptoms, and hallucinatory experiences are motivations for inappropriate use of over-the-counter drugs, and that sharing these experiences on SNS may form connections between users with similar interests.

Based on the above research results, our research group's proposed opinion on designating ingredients of " pharmaceuticals suspected to be abused " is

as follows.

**Proposed opinion on designating ingredients of pharmaceuticals suspected to be abused**

1. Dextromethorphan and diphenhydramine have been the subject of numerous reports of over-the-counter drug use cases and information on poisoning due to intentional ingestion, and health damage associated with abuse can also be confirmed in the literature, so they should be immediately designated as " pharmaceuticals suspected to be abused "

2. Although there are only a limited number of case reports of caffeine dependence, there have been reports of poisoning due to intentional ingestion and the appearance of abnormal electrocardiograms, so some form of sales restriction is necessary. However, there are a huge number of over-the-counter drug products that contain caffeine, and we believe it is not realistic to uniformly designate them as " pharmaceuticals suspected to be abused " like other ingredients. Since only a small number of products are abused, we believe it is necessary to request that the pharmaceutical companies that manufacture and sell the products issue warnings and take measures to prevent abuse.

3. Allylisopropylacetylurea is not used internationally as a medicine, and there is little information on the health effects of abuse, but a certain number of cases have been reported by domestic medical institutions specializing in addiction. In the future, additional tests will be required through basic research to evaluate the health effects of the ingredient, such as its addictive nature. It is also necessary to consider the appropriateness of approving it as a medicine, including bromovalerylurea, which has already been designated as a " pharmaceuticals suspected to be abused "

March 2025

**Principal investigator: Takuya Shimane, MPH, PhD.**

Department of Drug Dependence Research, National Institute of Mental Health, National Center of Neurology and Psychiatry