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## Alcohol Addiction of Methamphetamine Abusers in Japan

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**ABSTRACT:** Fifty-eight methamphetamine (MAMP) abusers were surveyed to demonstrate the types and nature of MAMP abuse. In-depth interviews using psychophysiological techniques assessed the subjects to be truthful or deceptive about their abuse histories. Research diagnostic criteria determined the subjects clinical symptoms. The results show that three factors characterize MAMP abuse: significant correlation was found between the years of abuse; the manifestation of somatic or mental disorders or both, and alcohol (Alc) addiction. MAMP abusers who were nondrinkers or light drinkers developed a tendency to dislike Alc after MAMP abuse, while there was no change in Alc consumption in heavy drinkers.

The findings suggest that the combined abuse of MAMP and Alc aggravates somatic and mental disorders and that Alc plays an important role in the fatal effect of MAMP, especially from small doses. This provides support for the synergistic effects between MAMP and Alc. Coadministration of MAMP and Alc appears to produce long-acting and more complicated changes in the brain's neurotransmitter function.

**KEYWORDS:** pathology and biology, methamphetamine, alcohol, abuse, drinking behavior, neurotransmitter

The effects of methamphetamine (MAMP) in decreasing fatigue and in heightening physical and mental abilities made its abuse among Japanese people widespread after the end of the Second World War. Since the Stimulant Regulations were legislated in 1951, MAMP abuse in Japan has declined greatly. However, cases of MAMP abuse have become increasingly prevalent during the past ten years. Multiple abuse involving the combined administration of different drugs has caused severe and complex psychedelic effects and interactions. In cases of abuse involving sedatives, narcotics, tranquilizers, volatile solvents, and so forth, it has been well known for the past five years or so that most drug abusers have a tendency to try any or all drugs, singly or in combination.

The current increase in alcohol (Alc) consumption might cause two types of abuse patterns—one primarily concerned with the effects of MAMP, and the other with the effects of Alc. Most users try to make the drugs act as true antagonists [1]. They commonly anticipate that MAMP neutralizes the depressant effects of Alc, while the excitability produced by MAMP is alleviated by Alc. The types of abuse patterns involving Alc and MAMP are not uncommon and are probably more widespread than has been previously supposed.

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However, few systematic studies have dealt with the interaction of MAMP or amphetamine (AMP), which has almost the same pharmacological characteristics as MAMP [2] and Alc, in spite of the widespread use of both.

The range of physiological interactions between MAMP (AMP) and Alc covers a broad spectrum, including antagonistic or synergic effects [3]. The interaction of MAMP (AMP) and Alc varies more widely in most psychomotor performance situations. Since MAMP (AMP) improves psychomotor performance and Alc impairs it, one would postulate that the combination of them would produce performance intermediate between the two drugs. The performance experiments for both animals [4–6] and humans [7–8], however, indicate more complex results. Many studies found that acute drug treatment with combinations of stimulants such as MAMP and depressants such as Alc would produce intermediate or antagonistic effects between the two drugs [9–12]. On the other hand, when given MAMP in combination with Alc, no clear evidence of antagonism with Alc was demonstrable on the performance of human subjects stressed with a delayed audio feedback system [13] and on mental task performance situations [14]. A performance task paradigm of dogs treated with moderate doses of Alc and AMP shows enhancement of excitability when compared with either drug alone [15]. These results reveal a great contradiction due to a tendency to lump experimental results in acute drug treatment with dose-related dependency and to greater complexities of interaction across a greater range of measures. Thus, the interaction of these two drugs would not reflect a straight depressant/stimulant antagonism.

The situation is further complicated by the fact that mild depressant effects of Alc are manifested behaviorally as hyperexcitability (disinhibition), in which case the interaction effect with MAMP (AMP) may be contradictory.

In the interaction of Alc (a central nervous system depressant) with central nervous system stimulants (MAMP/AMP), the dosage levels of both drugs become critical since, obviously, the effects of a small dose of Alc and a large dose of MAMP (AMP) will be quite different from those of a large dose of Alc and a small dose of MAMP (AMP). Alc treatment causes a dose-related reduction in AMP-induced excitability [16].

Finally, several fatal intoxication cases due to AMP (MAMP) demonstrate that smaller amounts of AMP (MAMP) than had been previously supposed were found to be the cause of death at autopsy [17–18]. It is postulated that the interaction of stimulant and depressant has some role in the induction of the fatal intoxication.

Given the results summarized above, there are clearly a number of reasons for continuing to examine the interactions between MAMP and Alc, to confirm whether Alc addiction of chronic MAMP abusers would be affected by coadministration of the drugs. In the present study of MAMP abuse and Alc addiction, a method of psychophysiological investigation of MAMP abusers was employed to confirm the relationship between the nature of MAMP abuse and Alc addiction.

## **Method**

### *Subjects*

Fifty-eight MAMP abusers who were accused of offenses involving the stimulant drug regulation rule were investigated through their historical backgrounds using a method involving in-depth interviewing with the technique of psychophysiological detection of deception. The subjects were screened from 85 MAMP abusers supplied according to the criteria; abusers were excluded as subjects when their statements concerning their background of MAMP abuse were deceptive according to the results of polygraph testing with the guilty knowledge technique for guilty information paradigm [19]. The phenyl-

methylaminopropane solid was detected by gas chromatograph mass spectrometry in the urine samples of each subject submitted to the district police at Hyogo Prefecture.

#### *Data Collected*

The period and degree of MAMP abuse for the subjects, their personal or criminal histories, and other data described in the text were collected. The subject's Alc preference and the extent of drinking behavior before, during, and after MAMP abuse were recorded. The somatic disorder, mental disorder, or both of each subject was diagnosed through results obtained from observations with psychophysiological interviewing, applying the research diagnostic criteria [20], and from interpretation of police records concerning their behavior since arrest.

#### *Data Analysis*

The correlation coefficient matrix of each of the collected items was obtained by the method of multiple variance analysis, applying the fourth class of quantification theory [21], and paired Student's *t*-tests were employed for significant differences. Nonparametric chi-square tests were performed for comparisons between the different inclinations to Alc and other factors. A difference of more than  $P < 0.05$  was considered statistically significant.

### **Results**

#### *Outline of MAMP Abusers*

The 58 MAMP abusers, including 7 females, investigated in this study were 19 to 55 years old (the mean age  $36 \pm 8$  years); 71% of them were unemployed.

They usually administered 20 to 30 mg (0.3 to 0.5 mg/kg) of MAMP at one time by intravenous injection. The average of their maximum dose was 3.36 times per day, and the mean interval of abuse was every 1.62 days.

These results compare well with previous data reporting the nature of MAMP abusers and would be sufficient for assessment of MAMP abusers.

#### *Criminality of MAMP Abusers*

Thirty-one percent (18 subjects) of MAMP abusers in this study had no convictions, excluding violating the Stimulant Regulation Rule; the remaining 69% (40 subjects) were ex-convicts of other crimes, including 40% (27.6% as a whole) with property offenses, 22.5% (15.5%) with criminal homicides, 15% (10.3%) with violent offenses, 15% (10.3%) with arsons, 2.5% (1.7%) with sexual offenses, and 5% (3.4%) with other crimes. Thus, MAMP abusers are liable to commit crimes against property, indicating that most of them were in need of money to purchase MAMP. An explosive tendency in the MAMP abuser's personality provides a high incidence of violent offenses, homicides, and arsons (Table 1).

#### *Correlation of Data*

The collected data for 58 MAMP abusers are listed in Table 2. This table presents the correlation coefficient values of each item. A strong correlation was found between the age (AG), the abusing years (PE), the maximum abuse dosage (MX), the mean interval of abuse (MN), the alcohol preference (AP), the existence of coadministration with Alc

TABLE 1—*Proportion of offenses in methamphetamine abusers.*

| Offense Categories       | Number (%) |
|--------------------------|------------|
| Property offenses        | 16 (27.6)  |
| Violent offenses         | 6 (10.3)   |
| Criminal homicide        | 9 (15.5)   |
| Sexual offenses          | 1 (1.7)    |
| Arson                    | 6 (10.3)   |
| Others                   | 2 (3.4)    |
| Only drug related crimes | 18 (31.0)  |
| Total                    | 58 (100.0) |

under MAMP abuse (CO), the Alc intake upon withdrawal of MAMP (IN), and the manifestation of somatic or mental disorders (SM).

There was, however, no correlation between the type of occupation (JB), the previous criminal record (RE), and the body weight (BD).

The SM correlated significantly with the PE ( $r = 0.430$ ), the CO ( $r = 0.388$ ), and the IN ( $r = 0.430$ ). The IN also had significant correlation with the AP ( $r = 0.673$ ) and the CO ( $r = 0.704$ ). The CO correlated significantly with the AP ( $r = 0.682$ ) and the PE ( $r = 0.389$ ). The correlation between the PE and the AG was significant ( $r = 0.494$ ). The MX correlated significantly with the PE ( $r = 0.320$ ), the MN ( $r = 0.297$ ), and the SM ( $r = 0.262$ ), while the MN correlated significantly with the CO ( $r = 0.264$ ) and the IN ( $r = 0.282$ ). These data prove that the characteristics of MAMP abusers are consistent with three factors: years of abuse with MAMP, MAMP-induced somatic and mental disorders, and coadministration of Alc with MAMP.

#### *Somatic and Mental Disorders of MAMP Abuse*

The manifestation ratio of somatic disorders, mental disorder, or both in MAMP abusers in this study was 37.9%, including 12.1% with somatic disorders—suspicious nature, aggressiveness, restlessness, insomnia or anorexia, and so forth—and 25.9% with mental disorders—paranoid delusion and visual and auditory hallucinations with amnesia. The total years of MAMP abuse for each subject related significantly with their age and varied from less than one year to more than eleven years. The mean abuse period for the normal MAMP abusers showing no somatic or mental disorders was 1.95 years. The MAMP abusers who complained of somatic disorders had abused drugs for an average of 3.18 years, and the average of abuse years for MAMP abusers who manifested mental disorders was 4.58 years. There was a significant difference in abuse years between the disorder and normal groups.

The number of abuse years influenced the development of somatic and mental disorders (Fig. 1). This factor was also significant in relation to the coadministration with Alc (Fig. 2).

These results indicate that not only long-term abuse of MAMP but also coadministration of Alc with MAMP would induce somatic and mental disorders.

#### *Alc Effects in MAMP Abuse*

The proportion of MAMP abusers who tried to coadminister Alc under the influence of MAMP was 34.5%, and 44.8% of MAMP abusers had taken Alc upon withdrawal from MAMP. Both the experience of simultaneous or alternative coadministration of

TABLE 2—Lower half matrix of correlation coefficients between data collected for 58 methamphetamine abusers.<sup>a</sup>

| Item | (1)<br>Age (AG) | (2)<br>Job (JB) | (3)<br>Criminal<br>Records (RE) | (4)<br>Abusing<br>Period (PE) | (5)<br>Maximum<br>Dosage<br>of Abuse<br>(MX) | (6)<br>Mean<br>Interval<br>of Abuse<br>(MN) | (7)<br>Alcohol<br>Preference<br>(AP) | (8)<br>Co-use<br>with<br>Alcohol<br>(CO) | (9)<br>Alcohol<br>Intake (IN) | (10)<br>Body<br>Weight (BD) | (11)<br>Somatic and<br>Mental<br>Disorders<br>(SM) |
|------|-----------------|-----------------|---------------------------------|-------------------------------|--|---|--------------------------------------|--|-------------------------------|-----------------------------|--|
| (1)  | 1.000           |                 |                                 |                               |  |   |                                      |  |                               |                             |  |
| (2)  | -0.043          | 1.000           |                                 |                               |  |   |                                      |  |                               |                             |  |
| (3)  | -0.330*         | 0.331*          | 1.000                           |                               |  |   |                                      |  |                               |                             |  |
| (4)  | 0.494**         | -0.133          | -0.329*                         | 1.000                         |  |   |                                      |  |                               |                             |  |
| (5)  | 0.138           | -0.158          | -0.179                          | 0.320*                        | 1.000  |   |                                      |  |                               |                             |  |
| (6)  | 0.077           | 0.059           | -0.224                          | 0.200                         | 0.297*                                       | 1.000                                       |                                      |  |                               |                             |  |
| (7)  | 0.075           | 0.134           | 0.089                           | 0.247                         | 0.108  | 0.124                                       | 1.000                                |  |                               |                             |  |
| (8)  | -0.065          | 0.170           | 0.069                           | 0.389**                       | 0.209  | 0.264*                                      | 0.682**                              | 1.000                                    |                               |                             |  |
| (9)  | 0.047           | 0.079           | 0.026                           | 0.255                         | 0.099  | 0.282*                                      | 0.673**                              | 0.704**                                  | 1.000                         |                             |  |
| (10) | 0.019           | 0.116           | 0.170                           | 0.008                         | -0.110                                       | -0.126                                      | 0.191                                | 0.134                                    | 0.024                         | 1.000                       |  |
| (11) | 0.261*          | -0.168          | -0.401                          | 0.430**                       | 0.262*                                       | 0.193                                       | 0.281*                               | 0.388**                                  | 0.406**                       | -0.203                      | 1.000  |

<sup>a</sup>Significant differences were estimated by paired Student's *t*-test: \* =  $P < 0.05$ ; \*\* =  $P < 0.01$ .

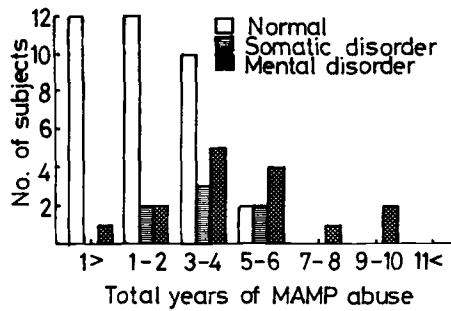


FIG. 1—Distribution of methamphetamine (MAMP) abusers with somatic and mental disorders according to total years of MAMP abuse. The length of MAMP abuse was associated with increased frequency of somatic and mental disorders.

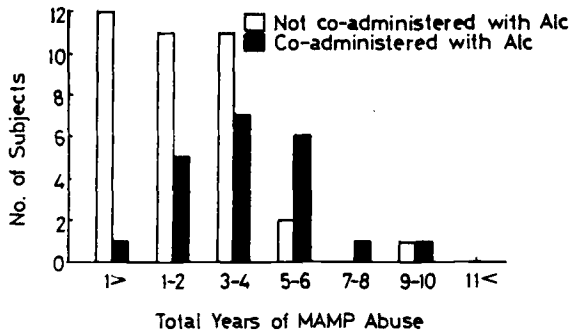


FIG. 2—Distribution of methamphetamine (MAMP) abusers classified according to their experiences with the coadministration of alcohol (Alc) under the influence of MAMP. Longer lasting abuse produced an increase in coadministration experiences of Alc and MAMP.

Alc and MAMP significantly increased the manifestation rate of somatic and mental disorders (Fig. 3). These results indicate that Alc would promote MAMP-induced psychosis.

*Alcohol Addiction in MAMP Abuse*

The results show that 36.2% of MAMP abusers had no preference for Alc, and of these 95.2% (34.5% as a whole) did not drink Alc under the influence of MAMP; 85.7% (31.0% as a whole) had not taken Alc upon withdrawal of MAMP. The 27.6% of MAMP abusers who had light preference for Alc included 87.5% (24.1% as a whole) who had not coadministered with Alc, and 68.8% (19.0% as a whole) who had not tried to take Alc on withdrawal of MAMP. On the other hand, of the remaining 36.2% who preferred Alc, 19.0% (6.9% as a whole) had not coadministered Alc, and 14.3% (5.2% as a whole) had not taken Alc after MAMP abuse; consequently, 81% (29.3% as a whole) of MAMP abusers who preferred Alc had coadministered with Alc, and 85.7% (31.0% as a whole) had continued to take Alc upon withdrawal of MAMP. These results are summarized in Table 3.

In the light drinking group of MAMP abusers, there was a tendency to avoid Alc. However, a strong tendency to Alc remained in the heavy drinking group of MAMP abusers.

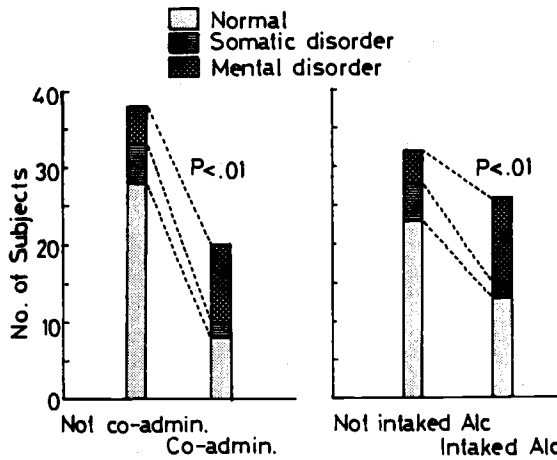


FIG. 3—Frequency of methamphetamine (MAMP) abusers with somatic and mental disorders according to experience with the coadministration of alcohol (Alc) under the influence of MAMP (left) and to Alc intake upon withdrawal of MAMP (right). Significant differences ( $P < 0.01$ ) between the manifestation of somatic and mental disorders and the simultaneous and alternative coadministration of Alc and MAMP were indicated.

TABLE 3—Frequency of exposure to Alc under the influence of MAMP and during withdrawal of MAMP in MAMP abusers, classified as heavy (HD), light (LD), and nondrinkers (ND).<sup>a</sup>

|   | Heavy<br>Drinker | Light<br>Drinker | Non-Drinker |
|---|------------------|------------------|-------------|
| Number of Subjects                                | 21               | 16               | 21          |
| Administration of Alc under the influence of MAMP | 17               | 2                | 1           |
| Intake of Alc during withdrawal of MAMP           | 18               | 5                | 3           |

<sup>a</sup>Frequency of simultaneous or alternative coadministration of Alc and MAMP decreased significantly ( $P < 0.1$ ) both in the LD and ND group, while the strong tendency of Alc preference in the HD group endured.

**Discussion**

Data collected from the background survey of MAMP abusers indicated that they described three factors that correlated significantly.

The effects of long-term abuse of MAMP, consistent with previous findings [22–24], demonstrate that nonpsychotic individuals who abuse MAMP manifest a somatic and/or mental disorder that is very similar to the hypersensitivity of stress.

In addition, the data presented indicate no role for the intermediate or antagonistic effects between MAMP and Alc. The combined effects of MAMP and Alc seemed to enhance each individual drug's effect. This result supports the finding in metabolic studies that Alc treatment markedly inhibits the hydroxylation of AMP [25] and causes an increase in the concentrations of AMP in the brain [26] or internal organs [27] in acute drug treatment in rats. Some clinical reports also emphasize the conclusion that the synergistic effect of MAMP and Alc is apparently a reality. Several instances of increased excitability occurred in inebriated patients who had concomitantly taken AMP [28–29].

Of greatest interest, however, is the finding that MAMP has no effect on Alc addiction in MAMP abusers. Most of MAMP abusers who were heavy drinkers continued to use Alc during MAMP abuse (coadministered with Alc under the influence of MAMP or drank Alc upon withdrawal of MAMP), while the MAMP abusers who were light drinkers or nondrinkers began to avoid Alc after injection of MAMP. This finding signifies that not only do chronic MAMP abusers develop the psychotomimetic effects of MAMP, but also a longer abuse period increases the frequency of Alc consumption by MAMP abusers. No specific effect of MAMP is shown on the native inclination of Alc preference.

Though individual differences in Alc sensitivity vary in alleviating the AMP (MAMP) induced excitability, AMP or MAMP abusers who are addicted to Alc endure their own inclination to drink even after AMP (MAMP) administration, while those who have a light or no addiction for Alc stop drinking.

It is possible to speculate on Alc preference and MAMP abuse through behavioral mechanisms. The nature of Alc addiction develops reinforcing properties in that Alc ingestion reduces the stressful anxiety or tension, and consequently it is easy to associate the psychotropic action of Alc accordingly. Exposure to Alc is an euphoria-inducing experience which would lend itself to Alc preference. On the other hand, MAMP (AMP) has the severe effect of creating a psychic dependence which may produce a sort of pleasure, namely that arising from the relief of discomfort caused by abstinence. These euphoric experiences induced by either MAMP (AMP) or Alc alone would therefore alternate with each other in the subjective effects of both drugs. Conscious of the illegality of MAMP (AMP) use, abusers, in particular, may moderate their MAMP-induced excitability, or they may be forced to compensate with Alc as a substitute for MAMP in pursuit of a similar subjective excitability induced by Alc. Thus, Alc and MAMP (AMP) serve as cross-dependency drugs. Also, continuous low-level AMP administration selectively increases Alc consumption [30], which suggests that the ordinary trend of chronic MAMP (AMP) abuse has adhered, as a result, to coadministration with Alc.

The Alc addiction in MAMP abusers has played a great role in the somatic and mental disorders induced by MAMP. Chronic MAMP (AMP) administration causes the schizophrenic syndrome named MAMP (AMP) psychosis [31], including hallucinations and illusions under clear consciousness, derived from a change of the brain's monoamine activities. MAMP causes a variety of changes in the central and peripheral neurotransmitter systems [32–35]. The repeated intermittent administration of MAMP (AMP) produces long-lasting change in the brain dopamine (DA), norepinephrine (NE), and serotonin (5-HT) systems. Chronic MAMP (AMP) treatment is associated with the inactivation of 5-HT systems, but more recent evidence of dopaminergic hyperactivity occurs after chronic MAMP administration, in addition to depletion of NE [36–37]. On the other hand, Alc creates so-called “alcoholics,” indicating that chronic ingestion of Alc may well have a profound effect on a large number of neurotransmitter-neuromodulator systems within the brain [38–39]. Chronic administration of Alc is associated with severe alterations in the turnover of brain NE, release of DA, and content of 5-HT. The coadministration of both drugs would lead to greater complexities of interaction on the somatic and mental syndromes, which may, in fact, be more common than has been previously supposed. Though there are various factors to consider in this interaction, for example, different dosages between the two drugs, the type of MAMP abuse with Alc consumption, the degree of neuronal damage caused by each drug, and so forth, an argument that the several neurotransmitter function systems after chronic treatment with both drugs are mutually apt to denature each other seems to be strongly supported. The uptake and release of NE may interfere in dopaminergic mechanisms, and the metabolism of DA may affect the serotonergic effect. Also, the depletion of 5-HT may moderate NE activity. These speculations could be confirmed through the measurement of each brain monoamine level after repeated applications of both drugs.



Coadministration of MAMP (AMP) and Alc may explain the fatal effects of MAMP (AMP) at relatively small doses which seems not to be at lethal levels. Several reports confirm that MAMP (AMP)-induced death was accompanied by physiological or behavioral changes, for example, anorexia, hyperpyrexia, and hyperexcitability [40–43]; these facts suggest that the MAMP (AMP) might cause depression of cardiovascular activities [44], from which the fatal effect of AMP (MAMP) may be derived. An acute treatment of both MAMP (AMP) and Alc in rats enhances the fatal effects [27,45], and some postmortem cases support these results [46]. The marked association of Alc intake in MAMP abusers, described in this study, would have an important role in the fatal effects of MAMP with relatively small doses; that is, MAMP abuse and Alc addiction are strongly associated with producing no effect on native Alc preference of MAMP abusers and also result in changes in the brain neurotransmitter systems. The implications of these speculations could be confirmed through chronic treatment with both drugs in more sophisticated experiments.

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