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Article

Differentiating Medicinal from Illicit Use in Positive Methamphetamine Results in a Pain Population

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In addition to illicit methamphetamine, there are prescription and over-the-counter medications that, if ingested, may yield positive methamphetamine (MAMP) results on laboratory urine drug tests. The purpose of the study is to estimate the prevalence of medicinal and illicit MAMP in the pain population using chiral analysis to determine the relative amounts of the *d* and *l*-MAMP enantiomers. This retrospective analysis included the LC-MS/MS results and prescriber provided medication histories of 485,889 de-identified urine specimens from patients treated for pain. Two groups of 100 specimens each were subjected to chiral analysis. Group 1 contained specimens that were MAMP positive and amphetamine negative. Group 2 contained randomly selected MAMP positive specimens. The overall MAMP positivity rate of the 485,889 specimens tested was 1.6%. The prevalence of MAMP medications based on reported medications and detection of *l*-MAMP in Group 1 and Group 2 was 44% and 6%, respectively. These data indicate that the use of both illicit and medicinal MAMP is found in this patient population, and that medicinal use is underreported in clinical histories. Therefore, clinical laboratories should provide on request chiral analysis to aid in differentiating illicit and medicinal MAMP.

Introduction

Methamphetamine (MAMP) is a drug of abuse in the United States that is detected by urine drug testing (1). Abuse of this drug quickly escalated in the 1980s, following the adoption by clandestine laboratories of simplified synthetic methods, making the drug inexpensive and readily available (2). MAMP is a highly addictive central nervous system (CNS) stimulant that produces a euphoric high followed by restlessness, agitation, dysphoria, paranoia and in extreme cases, psychosis. Systemic effects can be life-threatening and include increased body temperature, blood pressure and heart rate. Long-term users often appear to have aged prematurely. Over time, with the development of physical and mental deficits, the user may be unable to function in society (1, 3, 4).

The concomitant use of MAMP and prescribed opioid and anxiolytic medications can have serious implications for a patient's health (1, 3, 4). Therefore, patients on chronic opioid therapy are asked to sign treatment agreements stating that they will not use illicit substances such as MAMP (5–7). The finding of MAMP on a urine drug test may have severe consequences for the patient that go beyond health concerns, including potential dismissal from a physician's practice, loss of employment and loss of reputation (4, 8). Thus, correct interpretation of these results is critically important.

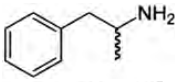
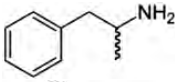
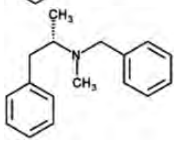
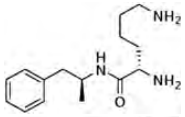
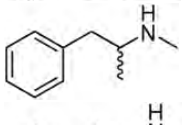
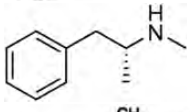
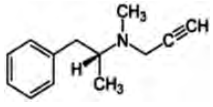
The interpretation of results is complicated by the fact that MAMP is both a prescription medication and an illicit substance of abuse (8, 9). Although the vast majority of reported positives are the result of illicit use, a small but significant number of MAMP positives will result from the use of medications that either contain or can be metabolized to MAMP. Routine mass spectral confirmatory methods do not distinguish between MAMP detected following illicit or medicinal use. To determine whether illicit use has occurred, the physician must first rule out the use of these medications. In the absence of a medication history, chiral analysis can often rule out illicit use. Other attributes of these drugs, including metabolite/parent drug ratios and total MAMP concentrations, are also indicators of which drug was used, but are much less specific and reliable. These do, however, provide clues to the origins of the drug.

Chiral analysis is a specialized analytical technique used to identify the enantiomeric compositions of drugs and their metabolites. MAMP medications can be eliminated from the body in two forms: the dextrorotary (*d*) and/or levorotary (*l*) enantiomer. Both forms have the same elemental composition but differ in their orientation at the asymmetric carbon, resulting in mirror image enantiomers with distinct pharmacological properties. Unlike routine mass spectral procedures, chiral analysis is able to identify this subtle structural difference, which can often confirm whether illicit *d*-MAMP or a *l*-MAMP medication was used, as discussed in the following paragraphs.

The *d*-form of the drug is a powerful CNS stimulant and the abused form of the drug (10, 11). Illicit methamphetamine contains either *d*-MAMP or a racemic mixture of the *d* and *l*-forms. *d*-MAMP is also found in Desoxyn and is a metabolite of Didrex (benzphetamine), as shown in Table I (12, 13). The *l*-form has low CNS activity, and consequently, a low abuse potential, but is an effective vasoconstrictor and used in the Vicks Vapor Inhaler (Vicks, Cincinnati, OH) as a nasal decongestant. When packaged in this way, the *l*-form is listed as the pseudonym "levmetamfetamine." *l*-MAMP is also a metabolite of selegiline (Emsam, Eldepryl and Zelapar) and some additional medications prescribed outside the United States (Table I) (14–16).

Results for a chiral analysis are expressed as the percentage of the *d*-enantiomer relative to the total amount of MAMP present. Federal workplace drug testing programs have established a threshold of 20% *d*-MAMP to distinguish between sources (17). For example, a chiral result of greater than or equal to 20% of *d*-MAMP would indicate the use of Desoxyn, Didrex or illicit *d* or *d*/*l*-MAMP. A chiral result of less than 20% of *d*-MAMP (or greater than 80% *l*-MAMP) indicates the use of Vicks or selegiline. The accuracy of chiral testing is limited by the optical purity of the derivatization reagent used in the analysis, which is typically between 95 and 99% *l*-enantiomer. The analysis of a specimen containing 100% *d*-MAMP using a reagent with an optical purity of 95% results in a finding of

Table I
AMP and MAMP Medications

Drug	Indicated use	Metabolite of	Metabolizes to	Brand names	Recommended dose	Structure
d-AMP	Narcolepsy Attention deficit hyperactivity disorder (ADHD)	Benzphetamine *d*-MAMP Lisdexamfetamine	N/A	Adderall Dexedrine Dextrostat	Adderall: 2.5–40 mg per day* Dexedrine: 5–40 mg per day*	
l-AMP	N/A	*l*-MAMP Selegiline	N/A	N/A	N/A	
Benzphetamine	Exogenous obesity	N/A	*d*-AMP *d*-MAMP	Didrex	Didrex: 25–150 mg per day	
Lisdexamfetamine • *l*-Lysine-*d*-amphetamine	ADHD	N/A	*d*-AMP	Vyvanse	Vyvanse: 30–70 mg per day	
d-MAMP • *d*-Desoxyephedrine • Methylamphetamine	ADHD in children Exogenous obesity	Benzphetamine	*d*-AMP	Desoxyn	Desoxyn: 20–25 mg per day for ADHD 5 mg before meals for obesity	
l-MAMP • *l*-Desoxyephedrine • Levodesoxyephedrine • Levmetamfetamine	Nasal decongestant	Selegiline	*l*-AMP	Vicks Vapor Inhaler	Vicks Vapor Inhaler: Approximately 6 mg/day†	
Selegiline • *l*-Deprenyl	Parkinson's disease Major depressive disorder	N/A	*l*-AMP *l*-MAMP	Eldepryl Zelapar Emsam Patch	Eldepryl: 10 mg per day Zelapar: 2.5 mg per day Emsam Patch: 6–12 mg per day	

*Daily dosage varies with indicated use.
†Vicks packaging recommends use no more than every two hours, two inhalations per nostril. The product delivers between 0.04 to 0.150 mg per inhalation.

95% *d*-MAMP. This explains why chiral results for specimens containing all of one or the other form are usually reported to contain slightly less than the known amount.

MAMP is metabolized by hepatic microsomal enzymes to amphetamine (AMP), resulting in the urinary elimination of AMP and unchanged MAMP. Differences in the metabolism of MAMP medications and their metabolites result in AMP/MAMP concentration ratios characteristic of the specific drug, which provides clues to their origins. For example, Vicks is eliminated with a low AMP/MAMP ratio because the *l*-MAMP contained in this product is metabolized at a slower rate than *d*-MAMP (8–11).

Reported metabolite ratios ([AMP]/[MAMP]) for MAMP medications and illicit MAMP from highest to lowest are as follows: benzphetamine (0.53–11.17) > selegiline (0.28–0.36) > Desoxyn (0.1–2.6) > illicit MAMP (0.04–0.37) > Vicks (0.0–0.12) (18–21). The variation in these ratios is the result of many factors, including, but not limited to, the time of administration and individual metabolic differences. In addition, concomitant use of AMP medications will produce higher than expected metabolite ratios because these drugs are eliminated as AMP. AMP medications are commonly prescribed in pain practices and include amphetamine, Adderall, Adipan, Dexedrine, Dextrostat and Vyvanse.

High MAMP concentrations can sometimes be used to rule out some MAMP medications. Although low drug concentrations can result from either medicinal or illicit use, urinary excretion studies have shown that higher concentrations are more indicative of illicit use and generally exclude the use of Vicks, selegiline or benzphetamine when these medications are used as prescribed. Desoxyn is an exception, which produces relatively high urinary concentrations following therapeutic use that are similar to concentrations observed following the use of illicit *d*-MAMP (9, 19, 20, 22).

Much of the knowledge regarding the interpretation of MAMP results comes from studies performed with active duty military service personnel in the 1990s. These are primarily healthy young men and women under the age of 25 that take few, if any, medications. Less than 1% of all positive MAMP tests from this group are the result of the *l*-form of the drug (23). The positivity rate for the *l*-form of the drug in patients treated for chronic pain has not been previously measured, but may be higher because these patients frequently have comorbidities that require treatment with multiple medications.

The purpose of this study was to characterize positive MAMP results in the population of patients with pain using new analytical and physician-provided prescription data. These data should provide a context for physicians to refine their interpretation of MAMP results and to develop a process for improved clinical decision-making.

Methods

Participants

The study cohort included patients treated with opioid therapy for chronic pain. Urine specimens were collected from these

patients at physician offices and shipped overnight via UPS or FedEx to Millennium Laboratories (San Diego, CA). The specimens were subsequently tested for prescribed medications and illicit drugs by liquid chromatography–tandem mass spectrometry (LC–MS-MS) as requested by the physician. This research was approved by the Aspire Independent Review Board (Santee, CA).

Test methods

A retrospective analysis was conducted by Millennium Research Institute using the prescription list and LC–MS-MS drug testing results for 485,889 de-identified urine specimens submitted by pain management physicians to Millennium Laboratories between May and November of 2011 (the pain cohort). Using the Millennium Laboratories test database, which includes the quantitative data for all tests performed and the physician-reported prescription histories, the analysis was performed by filtering for the desired criteria in Excel format. The LC–MS-MS methods used by Millennium Laboratories have been described previously (24).

The pain cohort was filtered to identify patients with the MAMP medications benzphetamine (Didrex), selegiline (Eldepryl, Emsam and Zelapar), or MAMP (Desoxyn or Vicks Vapor Inhaler) with their quantitative AMP and MAMP LC–MS-MS results. Separately, the pain patient cohort was filtered again to identify all specimens containing MAMP at a concentration above the laboratory reporting threshold of 100 ng/mL, from which the positivity rate, concentration range and median concentrations were calculated.

In addition, two groups of 100 specimens each were randomly selected from the pain cohort and retrospectively analyzed to determine the enantiomeric composition of MAMP in each specimen. The chiral analysis was performed by SED Laboratories (Albuquerque, New Mexico), a Clinical Laboratory Improvement Amendments (CLIA) and Substance Abuse and Mental Health Services Administration (SAMHSA) certified drug testing laboratory (SED Laboratories ceased operations in July 2012). Group 1 contained specimens that were positive for MAMP (>100 ng/mL) and negative for AMP (<100 ng/mL). This group was selected to estimate the effectiveness of the federal workplace reporting protocol in eliminating reported positives for *l*-MAMP. Group 2 contained specimens that were positive for MAMP (>100 ng/mL) without considering the AMP concentration. This group was selected to be representative of all MAMP positives and provides an estimate of the rate of illicit and medicinal MAMP use in the pain cohort. The physician-reported medications for each specimen were reviewed for MAMP medications.

Enantiomer analysis was performed by gas chromatography–mass spectrometry (GC–MS) using an Agilent model 6890/5975 GC-MSD equipped with a 15 m, 5% phenylmethyl silicone capillary column. Specimen aliquots (2 mL) were buffered to pH 9.1 and treated with sodium periodate to oxidize hydroxylated amines (ephedrine, pseudoephedrine and phenylpropanolamine) and to remove these potential interferants.

After completion of the oxidation step, the pH was adjusted with the addition of saturated sodium carbonate and aliquots were extracted using butyl chloride. The phases were separated by centrifugation, the butyl chloride was transferred to screw top tubes and 50 μL 0.1M *N*-triflouroacetyl-L-prolyl chloride (L-TPC) was added, the tubes were sealed and derivatized for 20 min at 55°C. The extracts were transferred to injection vials and analyzed by GC–MS in selected ion mode, in which m/z 251 and 258 were monitored for MAMP and the internal standard (MAMP D14), respectively.

The *d* and *l*-enantiomers were chromatographically resolved using this method. An unextracted standard, a calibrator containing 250 ng/mL of *d*-MAMP, 250 ng/mL of *l*-MAMP and controls (negative and positive) were analyzed with each batch of specimens. The percentage of *d*-enantiomer was calculated using the area counts of the *d* and *l*-peaks as follows:

$$\frac{d\text{-MAMP area counts}}{d\text{-MAMP area counts} + l\text{-MAMP area counts}} \times 100 = \%d\text{-MAMP}$$

Results and Discussion

The MAMP positivity rate (MAMP positives/number of specimens tested) in the pain cohort was 1.6%. The median MAMP concentration was 2,782 ng/mL and the range was 100 ng/mL to greater than 100,000 ng/mL, the assay cutoff and upper limit of linearity, respectively. The lower limit of quantitation is 50 ng/mL for both AMP and MAMP.

A total of 54 specimens (0.01%) in the pain cohort was reported with MAMP medications, compared with 8,210 specimens (1.6%) reported with AMP medications. All MAMP medications were represented, with the exception of Eldepryl, although it may have been reported as generic selegiline. Each of the MAMP medications contained examples of specimens that were MAMP positive. In the case of Vicks, only one specimen was found to contain AMP (4,801 ng/mL) and MAMP (71,704 ng/mL), but the concentrations and metabolite ratio were not consistent with reported values following Vicks use (20, 22). The reported use of Vicks by this patient may have been an attempt at deception. In the authors' experience, this is a fairly common occurrence. The LC–MS-MS analytical data and AMP/MAMP ratios for these specimens are listed in Table II.

The highest MAMP concentration for patients on benzphetamine was 5,460 ng/mL. This compares to a peak MAMP urinary concentration of 952 ng/mL that was reported in a single dose study by Cody *et al.* of 10 subjects taking 50 mg of benzphetamine (19). Higher concentrations in patients reporting benzphetamine may indicate further assessment for chronic benzphetamine use. Cody *et al.* also reported a much higher AMP/MAMP ratio for benzphetamine than any of the other MAMP medications examined. Patients on benzphetamine typically have AMP concentrations that exceed MAMP, and consequently, an AMP/MAMP ratio greater than 1.0, compared to the AMP/MAMP ratio of 0.2 typically observed for *d*-MAMP. This higher AMP/MAMP ratio is the result of the metabolism of two benzphetamine metabolites, *d*-MAMP and desmethybenzphetamine. The pattern was evident in all but one specimen (Specimen 1) of the Didrex/benzphetamine specimens listed in Table II.

Table II
Specimens with Listed MAMP Medications, LC–MS-MS Results and Calculated AMP to MAMP Ratios in the Pain Cohort

Specimen	Medications	AMP (ng/mL)	MAMP (ng/mL)	AMP/MAMP ratio	Specimen	Medications	AMP (ng/mL)	MAMP (ng/mL)	AMP/MAMP ratio
1	Benzphetamine	261	4,013	0.07	28	Methamphetamine (Desoxyn)	655	16,556	0.04
2	Benzphetamine	3,834	2,697	1.42	29	Methamphetamine (Desoxyn)	2,765	12,966	0.21
3	Benzphetamine	699	239	2.92	30	Methamphetamine (Desoxyn)	403	3,251	0.12
4	Benzphetamine	<50	<50	—	31	Methamphetamine (Desoxyn)	236	2,505	0.09
5	Benzphetamine	<50	<50	—	32	Methamphetamine (Desoxyn)	215	1,607	0.13
6	Benzphetamine (Didrex)	12,273	5,460	2.25	33	Methamphetamine (Desoxyn)	409	1,424	0.29
7	Benzphetamine (Didrex)	5,400	2,295	2.35	34	Methamphetamine (Desoxyn)	110	1,034	0.11
8	Benzphetamine (Didrex)	5,140	1,433	3.59	35	Methamphetamine (Desoxyn)	186	671	0.28
9	Benzphetamine (Didrex)	14,973	957	15.65	36	Methamphetamine (Desoxyn)	235	599	0.39
10	Benzphetamine (Didrex)	3,264	783	4.17	37	Methamphetamine (Desoxyn)	50	238	0.21
11	Benzphetamine (Didrex)	8,038	687	11.70	38	Methamphetamine (Desoxyn)	150	<50	—
12	Benzphetamine (Didrex)	2,665	660	4.04	39	Methamphetamine (Desoxyn)	67	<50	—
13	Benzphetamine (Didrex)	5,066	381	13.30	40	Methamphetamine (Desoxyn)	61	<50	—
14	Benzphetamine (Didrex)	69	57	1.21	41	Methamphetamine (Desoxyn)	<50	<50	—
15	Benzphetamine (Didrex)	12,081	<50	—	42	Methamphetamine (Desoxyn)	<50	<50	—
16	Selegiline (Emsam)	650	1,402	0.46	43	Methamphetamine	1,616	10,570	0.15
17	Selegiline (Emsam)	429	1,057	0.41	44	Methamphetamine	0	0	—
18	Selegiline (Emsam)	315	732	0.43	45	Methamphetamine	0	0	—
19	Selegiline (Emsam)	227	468	0.48	46	*l*-MAMP (Vick's Inhaler)	4,801	71,704	0.07
20	Selegiline (Emsam)	150	333	0.45	47	*l*-MAMP (Vick's Inhaler)	<50	<50	—
21	Selegiline (Emsam)	<50	76	—	48	*l*-MAMP (Vick's Inhaler)	<50	<50	—
22	Selegiline (Emsam)	84	<50	—	49	*l*-MAMP (Vick's Inhaler)	<50	<50	—
23	Selegiline (Zelapar)	218	601	0.36	50	*l*-MAMP (Vick's Inhaler)	<50	<50	—
24	Selegiline (Zelapar)	123	363	0.34	51	*l*-MAMP (Vick's Inhaler)	<50	<50	—
25	Selegiline	141	328	0.43	52	*l*-MAMP (Vick's Inhaler)	<50	<50	—
26	Selegiline	100	<50	—	53	*l*-MAMP (Vick's Inhaler)	<50	<50	—
27	Selegiline	<50	<50	—	54	*l*-MAMP (Vick's Inhaler)	<50	<50	—

The highest MAMP concentration observed for any of the selegiline medications was 1,402 ng/mL for a patient on the Emsam transdermal patch. For the other reported selegiline medications, the highest level was 601 ng/mL for one patient on Zelapar. These levels are comparable to the peak MAMP urinary concentration of 1,010 ng/mL reported in a single dose study by Kim *et al.* of five subjects taking 10 mg of selegiline (20). A higher concentration of 5,420 ng/mL MAMP was reported in a case study of one individual on Eldepryl (18). Consistent with published literature, the current study reports higher AMP/MAMP ratios than *d*-MAMP following the use of selegiline (18, 20). Patients in the pain cohort using Emsam or selegiline fit this pattern. The higher AMP/MAMP ratio for this drug may be the result of the metabolic conversion to *l*-AMP from two selegiline metabolites, desmethylselegiline and *l*-MAMP.

MAMP concentrations for the patients prescribed Desoxyn or MAMP were higher than those of patients on the other MAMP medications. The highest concentration for the patients prescribed Desoxyn or MAMP, 16,556 ng/mL, compares to a peak urinary concentration of 18,468 ng/mL reported by Oyler *et al.* following the controlled administration of Desoxyn (21). The average AMP/MAMP ratio for patients on Desoxyn or MAMP was, on average, lower than the ratio for the patients on either selegiline or benzphetamine and consistent with published studies (19–21).

No specimens were positive for Vicks in the current study for comparison with published studies. Previous studies involving the controlled administration of Vicks in human subjects have produced peak urinary concentrations of up to 6,000 ng/mL (22).

This and other studies suggest that MAMP medications are unlikely to produce a positive result at high concentrations (18–20). In this study, with the exception of Desoxyn, none of the patients on MAMP medications produced a level above 10,000 ng/mL. In this sampling of the pain population, 31.2 % of all MAMP positives were above 10,000 ng/mL.

The results for Group 1 (MAMP positive, AMP negative) are presented in Table III. In this group, 43% of specimens ($n = 43$) were scored positive for *l*-MAMP and 57% of specimens ($n = 57$) were scored positive for *d*-MAMP. Consistent with the known metabolic differences in the enantiomers, the *l*-form was detected at a much higher rate than the representative sampling of all MAMP positives, as represented in Group 2. Under federal workplace reporting rules, all specimens in Group 1 would be reported negative for MAMP. With respect to the 43 *l*-MAMP positive specimens, the classification of these results as negative may be advantageous because it saves resources by removing many *l*-MAMP results from consideration that are likely to be from medicinal sources. However, the remaining 57 *d*-MAMP specimens in this group would also be reported negative. This reporting protocol may not be acceptable for programs that require the highest possible detection rates.

The results for Group 2 (MAMP positive, any AMP concentration) are presented in Table IV. In this group, 95% of specimens ($n = 95$) were scored positive for the *d*-MAMP enantiomer. Most contained more than 95% *d*-MAMP and 5% of specimens ($n = 5$) contained only *l*-MAMP. In addition to the five *l*-MAMP specimens, the *d*-MAMP result for Specimen 65 is probably the result of the reported MAMP medication Didrex, bringing the total of MAMP results due to MAMP medications in Group 2 to 6% of specimens ($n = 6$). Although this is a relatively small specimen set, it suggests a somewhat higher rate of medicinal MAMP use in the pain population than rates observed among military service personnel, 0.04% in one study (25).

MAMP or AMP medications were not reported for many specimens that, analytically, appear to be the result of their use.

Table III
Chiral and LC–MS-MS Results for Group 1 Specimens*

Specimen	AMP (ng/mL)	MAMP (ng/mL)	*d*–MAMP (%)	Specimen	AMP (ng/mL)	MAMP (ng/mL)	*d*–MAMP (%)	Specimen	AMP (ng/mL)	MAMP (ng/mL)	*d*–MAMP (%)	Specimen	AMP (ng/mL)	MAMP (ng/mL)	*d*–MAMP (%)
1	<50	5,758	96%	26	61	424	95%	51	84	222	97%	76	<50	153	94%
2	<50	1,248	97%	27	68	415	95%	52	<50	220	**2%**	77	<50	151	**2%**
3	95	1,127	96%	28	68	391	97%	53	<50	217	**1%**	78	<50	150	85%
4	92	807	97%	29	87	390	97%	54	<50	215	**2%**	79	<50	148	**2%**
5	<50	805	**1%**	30	<50	389	**2%**	55	<50	215	60%	80	<50	148	**2%**
6	60	783	88%	31	57	386	92%	56	<50	211	**2%**	81	<50	147	**15%**
7	<50	775	**1%**	32	<50	382	**2%**	57	95	205	51%	82	<50	138	96%
8	51	752	97%	33	74	341	97%	58	<50	202	97%	83	<50	137	37%
9	<50	744	**1%**	34	<50	328	**2%**	59	<50	200	**2%**	84	<50	135	**2%**
10	<50	709	97%	35	<50	318	96%	60	<50	199	**3%**	85	<50	135	75%
11	59	693	**2%**	36	<50	314	**2%**	61	75	199	96%	86	<50	134	**2%**
12	61	679	45%	37	<50	314	97%	62	<50	191	96%	87	<50	133	**1%**
13	64	669	**1%**	38	<50	312	96%	63	<50	187	**2%**	88	<50	131	56%
14	81	632	26%	39	<50	274	97%	64	<50	186	97%	89	<50	122	**1%**
15	<50	611	94%	40	76	269	96%	65	78	183	97%	90	62	121	96%
16	<50	562	96%	41	<50	268	**1%**	66	<50	182	95%	91	<50	110	97%
17	<50	558	**1%**	42	92	257	96%	67	75	181	23%	92	<50	109	**3%**
18	<50	552	90%	43	<50	252	**2%**	68	<50	179	**1%**	93	81	108	91%
19	52	552	**2%**	44	83	247	94%	69	<50	176	**1%**	94	<50	107	**2%**
20	<50	486	**3%**	45	76	246	97%	70	81	173	95%	95	79	107	96%
21	<50	473	42%	46	<50	239	**2%**	71	<50	170	84%	96	<50	106	**1%**
22	82	470	77%	47	<50	239	**1%**	72	<50	166	**2%**	97	73	103	94%
23	<50	468	88%	48†	50	238	97%	73	53	160	96%	98	<50	103	**2%**
24	<50	455	96%	49	<50	230	98%	74	<50	159	97%	99	<50	102	**2%**
25	<50	437	**2%**	50	<50	224	**2%**	75	58	158	**11%**	100	61	102	**10%**

*Note: Specimens with an AMP concentration below 100 ng/mL are reported negative for MAMP under workplace rules. Results in bold indicate *l*-MAMP specimens.
†Desoxyn was reported for Specimen 48.

Table IV
Chiral and LC–MS-MS Results for Group 2 Specimens with Randomly Selected MAMP Positive Samples*

Specimen	AMP (ng/mL)	MAMP (ng/mL)	*d*–MAMP (%)	Specimen	AMP (ng/mL)	MAMP (ng/mL)	*d*–MAMP (%)	Specimen	AMP (ng/mL)	MAMP (ng/mL)	*d*–MAMP (%)	Specimen	AMP (ng/mL)	MAMP (ng/mL)	*d*–MAMP (%)
1	572	>100,000	30%	26	2,422	5,930	96%	51	692	1,005	97%	76	154	270	96%
2	9,840	>100,000	97%	27	551	5,426	96%	52	427	1,000	**2%**	77	23	262	97%
3	16,584	>100,000	96%	28	679	5,238	97%	53	94	990	**3%**	78	1,023	261	97%
4	4,783	>100,000	96%	29	4,713	4,621	97%	54	218	980	97%	79	69	259	97%
5	1,484	79,743	97%	30	1,015	4,560	97%	55	3,235	946	88%	80	56	251	66%
6	13,112	62,967	97%	31	468	4,315	97%	56	207	891	97%	81	110	246	97%
7	17,757	55,097	97%	32	804	3,808	97%	57	1,488	836	97%	82	23,476	233	96%
8	11,169	51,010	96%	33	315	3,766	97%	58	1,293	778	62%	83	<50	228	97%
9	30,186	43,824	97%	34	1,091	3,389	96%	59	202	753	93%	84	300	219	97%
10	3,337	35,690	97%	35	539	3,028	97%	60	257	753	96%	85	85	217	82%
11	2,141	28,416	97%	36	3,419	2,935	96%	61	<50	737	**2%**	86	130	216	87%
12	3,562	25,673	97%	37	18	2,858	97%	62	<50	729	97%	87	<50	190	31%
13	2,711	24,608	97%	38	2,044	2,523	97%	63	267	728	97%	88	64	184	94%
14	3,906	20,571	97%	39	473	2,472	96%	64	290	725	96%	89	152	180	96%
15	14,796	19,103	97%	40	85,855	2,271	41%	65†	2,665	660	97%	90	98	173	100%
16	11,332	18,206	93%	41	1,371	2,214	97%	66	469	621	97%	91	37	172	97%
17	2,399	16,941	96%	42	3,030	1,660	96%	67	229	565	97%	92	148	169	97%
18	2,095	16,885	97%	43	399	1,609	94%	68	67	543	95%	93	<50	157	**1%**
19	848	11,442	96%	44	191	1,401	97%	69	254	523	97%	94	<50	156	86%
20	2,282	10,868	97%	45	6,711	1,356	97%	70	167	495	95%	95	158	149	94%
21	5,124	7,427	94%	46	238	1,274	97%	71	90	483	100%	96	<50	123	**0%**
22	2,260	7,367	96%	47	557	1,222	97%	72	3,119	436	100%	97	83	117	97%
23	1,013	6,416	96%	48	422	1,200	97%	73	180	397	96%	98	191	111	96%
24	644	6,350	96%	49	323	1,105	92%	74	81	360	97%	99	118	111	96%
25	1,009	6,323	96%	50	96	1,032	97%	75	404	354	96%	100	<50	103	96%

*Note: Results in bold indicate *l*-MAMP specimens.
†Didrex was reported for Specimen 65.

No MAMP medications (selegiline or Vicks) were reported for any of the 48 *l*-MAMP positives detected in both groups. Many additional specimens in Group 2 (e.g., Specimens 36, 40, 42, 45 and 82) have metabolite ratios that suggest the use of benzphetamine or concomitant use of an AMP medication. Although some of these specimens may also represent late phase elimination or individual variation in the metabolism of illicit MAMP, this does not appear to be true in all cases. Only one MAMP medication was reported in each group: Desoxyn for Specimen 48 in Group 1 and Didrex for Specimen 65 in Group 2. The underreporting of medication histories (both prescription and over the counter) was an unexpected finding. Thus,

medication histories alone were not useful in estimating the prevalence of MAMP medications for either group or for the pain cohort as a whole.

The majority of *d*-MAMP positive specimens in both groups contained over 95% of *d*-MAMP. Both tables also contain examples of specimens with *d* ratios in the 20–50% range, consistent with the use of racemic *d*-MAMP. The higher relative amount of *l* in many of these specimens is the result of the faster metabolism of the *d*-enantiomer. In Group 2, Specimen 1 is unusual because it contained 30% *d*-MAMP at a concentration of >100,000 ng/mL with a low metabolite ratio. The recent use of racemic MAMP could explain this finding. Other results suggest the use of medications in combination with illicit MAMP. Specimen 40 in Group 2 is also unusual because it contains 41% *d*-MAMP with a high relative amount of AMP, suggesting the combined use of AMP and racemic MAMP.

The following four clinical vignettes demonstrate how clinical histories, MAMP concentrations, AMP/MAMP ratios and chiral results can be used in combination to determine which drug was used.

Case 1

A 28-year-old male is a new patient receiving opioids for chronic back pain. Drug test results are positive for MAMP (26,528 ng/mL) and AMP (4,328 ng/mL) by LC–MS-MS. The patient reports the use of over-the-counter (OTC) "energy pills," diet aids, Vicks Vapor Inhaler and pseudoephedrine.

Case 1 interpretation

A review of the results with the laboratory confirms that OTC diet aids and pseudoephedrine will not give false positives for AMP or MAMP by LC–MS-MS. The high levels of MAMP in this patient are inconsistent with selegiline and Vicks, and the patient is not prescribed Desoxyn, selegiline or benzphetamine. The patient denies use of illicit MAMP. A chiral analysis finds 92% *d*-MAMP, confirming illicit use.

Case 2

A 68-year-old male is a new patient receiving opioids for chronic back pain. Drug test results are positive for MAMP (265 ng/mL) and AMP (105 ng/mL). No MAMP medications are reported, but the patient has a history of depression.

Case 2 interpretation

The low levels of MAMP and AMP could be the result of either illicit MAMP or an undisclosed MAMP medication, e.g., selegiline. Chiral analysis finds 5% *d*-MAMP (95% *l*-MAMP). A consult with the primary care physician reveals that the patient has been prescribed Emsam for depression, which is consistent with the results of the chiral analysis.

Case 3

A 55-year-old male is a new patient receiving opioids for diabetic neuropathic pain. Drug test results are positive for MAMP (3,624 ng/mL) and AMP (8,924 ng/mL). No MAMP medications are reported, but the patient has been treated by the primary care physician for obesity.

Case 3 interpretation

The high AMP/MAMP ratio suggests the use of benzphetamine. A consult with the referring physician reveals that the patient is still being treated for obesity and has a current prescription for Didrex (benzphetamine).

Case 4

A 36-year-old female is a new patient with a history of fibromyalgia and attention deficit disorder (ADD). Drug test results are positive for AMP (9,256 ng/mL) and negative for MAMP. There are no reported MAMP or AMP medications.

Case 4 interpretation

The finding of AMP in the absence of MAMP suggests the use of an AMP medication. A consult with the referring physician reveals that the patient has been prescribed Adderall (AMP) for the treatment of ADD.

Case 5

A 24-year-old male is an established patient with no history of drug use who is beginning long-term opioid therapy. Drug test results are positive for MAMP at 420 ng/mL and negative for AMP. Patient indicates the use of a Vicks Vapor Inhaler over a three-day period to treat persistent nasal congestion.

Case 5 interpretation

The finding of MAMP and the absence of AMP is consistent with the use of Vicks. Chiral analysis confirms the presence of only *l*-MAMP, which is consistent with the patient's reported use of Vicks.

Conclusions

This study found that the MAMP medications selegiline, benzphetamine, *d*-MAMP and *l*-MAMP are all used in this patient population and significantly contribute to the positivity rate for MAMP. The most important characteristics of urine drug test results that distinguish the users of MAMP medications and illicit MAMP are drug concentration and enantiomeric composition. With the exception of Desoxyn, MAMP medications were associated with urinary concentrations below 10,000 ng/mL. However, because only 31% of all MAMP results exceed this level, concentration alone was not found to be very useful in determining the source. To accomplish source determination, many specimens will also require chiral analysis and a careful review of the medication history. The analysis of Group 2 specimens found that 43% of specimens that would be reported negative under workplace reporting rules contained *l*-MAMP specimens. The adoption of this reporting method in the clinical laboratory significantly reduces the number of chiral tests ordered, in addition to the time required to evaluate MAMP results. Clinical laboratories and physicians may want to consider the benefits of this reporting method, which is not required in clinical testing, but mandated in workplace testing programs.

Currently, there are no formally established guidelines for the use of AMP/MAMP ratios or MAMP concentrations for the

evaluation of MAMP results. This is because of the high level of uncertainty associated with these parameters. Metabolite ratios for different medications can overlap over the time course of elimination. Their predictive value is further compromised by unreported concomitant use of AMP medications. However, metabolite ratios may be helpful in clinical decision-making when other factors are considered.

Similar to positivity rates reported by workplace drug testing programs, the rates for MAMP observed in the population of patients with pain are significant, and pain management physicians are regularly challenged with interpreting these results. The finding that 6% of MAMP positives are the result of prescription or OTC medications was surprising, and indicates that physicians should be alert to the possibility that these medications will occasionally result in positive findings. Chiral analysis is a well-established method that can resolve most cases, and laboratories should provide this test upon request. However, chiral analysis does not distinguish illicit use and the use of Didrex or Desoxyn. An accurate interpretation should include medication review and the use of the other interpretive tools reviewed here.

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