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Urinary Morphine Detection by Gas Chromatography–Mass Spectrometry for Assessing Methadone Treatment Adherence

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Abstract

Background: Opioid use disorder is a significant public health issue, and adherence to Methadone Maintenance Therapy (MMT) is critical for successful treatment. Self-reported adherence can be biased, so objective laboratory measures are valuable. Urinary morphine detection by Gas Chromatography–Mass Spectrometry (GC-MS) indicates recent illicit opioid use and may signal lower methadone adherence. This study examined the association between GC-MS-confirmed urinary morphine detection and methadone adherence in MMT patients.

Methods: This cross-sectional analytical study included 20 MMT patients at the PTRM Clinic of Gambir Public Health Center, selected by quota sampling. Urinary morphine was measured using GC-MS. Treatment adherence was assessed with a modified Morisky Medication Adherence Scale-8 (MMAS-8) and medical records. Data were analyzed using the Fisher–Freeman–Halton Exact Test, with Cramer's V describing the strength of association.

Result: Urinary morphine was detected in 2 participants (10%), while 18 (90%) had results below the detection limit. High, moderate, and low adherence were observed in 65%, 30%, and 5% of participants, respectively. The Fisher–Freeman–Halton Exact Test showed a statistically significant association between urinary morphine detection and methadone adherence categories ($p = 0.032$). Although Cramer's V was 0.733, this result should be interpreted with caution due to the small number of positive cases.

Conclusion: GC-MS-confirmed urinary morphine detection was significantly associated with lower methadone adherence and may complement behavioral and clinical assessments by providing objective evidence of recent illicit opioid use. These findings are preliminary, and larger multicenter longitudinal studies are needed to confirm their clinical relevance.

Keywords: Urinary Morphine, Treatment Adherence, Gas Chromatography–Mass Spectrometry

BACKGROUND

Opioid use disorder (OUD) is a significant global public health issue that contributes to morbidity, mortality, and socioeconomic burden worldwide, including in Indonesia (1–3). Persistent opioid misuse leads to adverse outcomes such as infectious diseases, psychiatric disorders, criminal behavior, and diminished quality of life. Despite the development of various treatment approaches, relapse rates remain high due to complex factors including psychological stress, insufficient social support, environmental influences, and limited engagement with treatment programs. Therefore, implementing effective long-term treatment strategies with reliable patient monitoring is critical to improving outcomes and reducing ongoing illicit opioid use.

Methadone Maintenance Therapy (MMT) is recognized as an effective, evidence-based intervention for opioid dependence and is a key component of harm reduction programs in many countries (4–6). In Indonesia, MMT is delivered through the Program Terapi Rumatan Metadon (PTRM), which seeks to reduce illicit opioid use, enhance quality of life, and mitigate the health and social consequences of opioid dependence (5,7). Sustained adherence to methadone treatment is associated with improved clinical stability, better psychosocial functioning, and reduced relapse rates. In contrast, poor adherence increases the risk of treatment discontinuation, recurrent opioid use, and adverse clinical outcomes (8).

Treatment adherence in MMT is commonly assessed using self-reported questionnaires, interviews, and attendance records. Adherence to MMT is typically assessed through self-reported questionnaires, interviews, attendance records, or clinical observations. While these methods are practical, they are vulnerable to recall bias, underreporting, and social desirability bias, which can compromise accuracy (9–11). Objective laboratory examinations can provide valuable supplementary information. Urine drug testing is frequently employed to detect recent opioid exposure, as urine contains measurable opioid metabolites and is straightforward to collect (11–13). Initial screening often utilizes immunoassays, but these may yield false-positive or false-negative results due to cross-reactivity with structurally similar compounds (15–18). Therefore, confirmatory testing with highly specific analytical techniques is recommended.ysis because of its high analytical sensitivity and specificity. GC-MS enables accurate identification of morphine and other opioid metabolites following chromatographic separation and mass spectral detection. (19–22) Detection of urinary morphine primarily reflects recent illicit opioid exposure and may provide objective evidence of possible opioid reuse during methadone treatment. Therefore, urinary morphine analysis should be interpreted as a toxicological indicator that complements, rather than replaces, behavioral assessment of treatment adherence.

Although urine drug testing is increasingly utilized in addiction medicine, there is limited evidence integrating toxicological confirmation of urinary morphine with behavioral assessment of methadone treatment adherence, especially in primary healthcare settings in Indonesia. Most prior studies have assessed adherence using behavioral or clinical measures alone or have focused solely on laboratory detection of opioid metabolites without evaluating their correlation with adherence (23,24). Combining these complementary approaches may offer a more comprehensive evaluation of patients undergoing methadone maintenance therapy and inform clinical decision-making in rehabilitation services.

This study aims to evaluate the correlation between GC-MS-confirmed urinary morphine detection and methadone treatment adherence among patients receiving Methadone Maintenance Therapy at the PTRM Clinic of Gambir Public Health Center. By integrating toxicological confirmation

of recent illicit opioid exposure with behavioral adherence assessment, the study intends to establish a more comprehensive approach for monitoring patients undergoing methadone maintenance therapy in a primary healthcare context.

METHODS

Study Design

An analytical observational design with a cross-sectional approach.

Sample/Participants

The study population comprised 35 patients actively enrolled in the Methadone Maintenance Therapy (MMT) program at the PTRM Clinic of Gambir Public Health Center. Of these, 20 patients meeting the inclusion criteria were recruited using a quota sampling technique. The independent variable was urinary morphine detection confirmed by GC-MS (detectable or non-detectable), and the dependent variable was methadone treatment adherence.

Data Collection

Data was utilized at the PTRM Clinic of Gambir Public Health Center, Central Jakarta, between December 2025 and April 2026. Initial urine drug screening was conducted at the Gambir Public Health Center Laboratory using a qualitative immunochromatographic strip test. Confirmatory analysis was subsequently performed using Gas Chromatography–Mass Spectrometry (GC-MS) at the Regional Health Laboratory (LABKESDA) of DKI Jakarta.

Urine samples (3.0 mL) were collected in sterile urine containers and stored at 2–4°C before transportation to the Regional Health Laboratory using a cool box with ice gel packs. Sample preparation included the addition of 50 µL nalorphine as the internal standard, followed by solid-phase extraction (C18 cartridge), enzymatic hydrolysis using Escherichia coli β-glucuronidase at 20°C for 90 min, extraction with tert-butyl methyl ether (TBME), and derivatization using 50 µL N-methyl-N-(trimethylsilyl) trifluoroacetamide (MSTFA) at 60°C for 15 min. GC-MS analysis was performed using an Agilent Technologies 7890A Gas Chromatograph coupled with a 5975C Mass Selective Detector operating in electron impact ionization mode (70 eV) with helium as the carrier gas. Chromatographic separation was achieved using a DB-5MS capillary column (30 m × 0.25 mm i.d., 0.25 µm film thickness). The oven temperature was programmed from 100°C (1 min), increased at 20°C/min to 280°C, and held for 10 min. Morphine was identified by its characteristic retention time (approximately 14.2 min) and confirmation of the target ions (m/z 429, 414, and 236) in selected ion monitoring (SIM) mode, following previously validated analytical methods for urinary opioid confirmation. The analytical method had a limit of detection (LOD) of 13.50 ng/mL.

Instruments

Treatment adherence was evaluated using a modified Morisky Medication Adherence Scale-8 (MMAS-8) questionnaire in conjunction with medical record review. The assessment encompassed behavioral adherence, attendance records, dose consistency, and substance use history. Adherence scores were expressed as percentages and classified as high (≥80%), moderate (60–79%), or low (<60%).

Data Analysis

Data were analyzed using the Statistical Package for the Social Sciences (SPSS). Descriptive statistics were used to summarize participant characteristics and study variables. The association between GC-MS-confirmed urinary morphine detection and methadone treatment adherence was analyzed using the Fisher–Freeman–Halton Exact Test, while Cramer's V was calculated to estimate

the strength of the association. Because of the small sample size and the limited number of participants with detectable urinary morphine, Cramer's V estimate was interpreted cautiously as an exploratory measure of effect size. A p-value <0.05 was considered statistically significant.

Ethical Consideration

This study received ethical approval from the Ethics Committee of Sekolah Tinggi Ilmu Kesehatan Nasional (No. 359/EC/KEPK/II/2026), and written informed consent was obtained from all participants before data collection.

RESULT AND DISCUSSION

RESULT

Twenty patients receiving Methadone Maintenance Therapy (MMT) at the PTRM Clinic of Gambir Public Health Center participated in this study. Urinary morphine was first screened with a qualitative immunochromatographic strip test, then confirmed by Gas Chromatography–Mass Spectrometry (GC-MS). The analytical method had a limit of detection (LOD) of 13.50 ng/mL. Treatment adherence was measured using a modified Morisky Medication Adherence Scale-8 (MMAS-8) and medical record review.

Urinary Morphine Analysis and Methadone Treatment Adherence

Figure 1 presents the results of urinary morphine analysis and methadone treatment adherence among patients receiving methadone maintenance therapy (MMT). Gas chromatography-mass spectrometry (GC-MS) confirmed that 18 patients (90%) had urinary morphine concentrations below the analytical detection limit (13.50 ng/mL), while 2 patients (10%) exhibited detectable morphine levels of 717.04 ng/mL and 554.34 ng/mL, respectively. Regarding treatment adherence, 13 patients (65%) demonstrated high adherence to methadone therapy, 6 patients (30%) exhibited moderate adherence, and 1 patient (5%) showed low adherence.

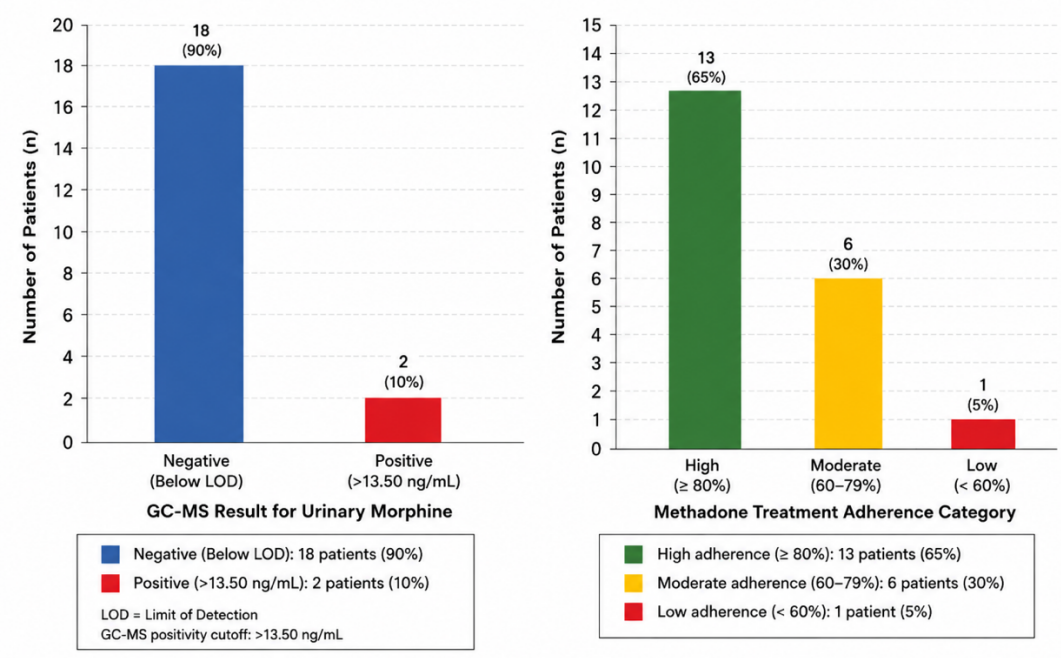


Figure 1.
Urinary Morphine Results Based on GC-MS Confirmation

Figure 2.
Methadone Treatment Adherence Categories

Notes: Adherence was assessed using a modified MMAS-8 questionnaire combined with medical record evaluation.
LOD = Limit of Detection; GC-MS = Gas Chromatography–Mass Spectrometry.

The graphical data indicate that patients with negative urinary morphine results generally demonstrate higher adherence to methadone therapy compared to those with positive morphine findings. High adherence was predominantly observed among patients with negative GC-MS results, while positive urinary morphine detection was associated with moderate or low adherence. These findings suggest that urinary morphine analysis via GC-MS may serve as an objective laboratory indicator for assessing treatment adherence and detecting potential opioid reuse in patients receiving methadone maintenance therapy.

Association Between Urinary Morphine Results and Treatment Adherence

Table 1 presents the association between urinary morphine results and methadone treatment adherence among patients undergoing Methadone Maintenance Therapy (MMT). GC-MS confirmation indicated that patients with negative urinary morphine results predominantly exhibited high adherence to methadone therapy. In contrast, positive urinary morphine findings were more frequently associated with moderate or low adherence. Of the 18 patients with negative urinary morphine results, 13 (72.2%) demonstrated high adherence and 5 (27.8%) moderate adherence; none exhibited low adherence. Among the two patients with positive urinary morphine results, one (50%) demonstrated moderate adherence and one (50%) demonstrated low adherence. No patients with positive urinary morphine findings were classified as highly adherent.

Table 1. Association Between Urinary Morphine Results and Methadone Treatment Adherence

Urinary Morphine Result	High Adherence	Moderate Adherence	Low Adherence	Total
Negative (n = 18)	13 (72.2%)	5 (27.8%)	0 (0%)	18 (100%)
Positive (n = 2)	0 (0%)	1 (50%)	1 (50%)	2 (100%)
Total	13 (65%)	6 (30%)	1 (5%)	20 (100%)

Table 2 presents the statistical analysis of the association between urinary morphine results and treatment adherence. The Fisher–Freeman–Halton Exact Test identified a statistically significant association between urinary morphine status and methadone treatment adherence ($p = 0.032$). The strength of this association, as measured by Cramer's V, was 0.733, which indicates a strong correlation between the variables. These results suggest that urinary morphine detection via GC-MS may function as an objective laboratory indicator for assessing adherence in patients receiving methadone maintenance therapy.

Table 2. Statistical Analysis of the Association Between Urinary Morphine Results and Treatment Adherence

Statistical Test	Value	p-value
Fisher–Freeman–Halton Exact Test	6.690	0.032
Cramer's V	0.733	—

DISCUSSION

Urinary Morphine Findings

The results indicate that most patients receiving Methadone Maintenance Therapy (MMT) at the PTRM Clinic of Gambir Public Health Center had negative urinary morphine outcomes following

confirmation with Gas Chromatography–Mass Spectrometry (GC-MS). This suggests that the majority of participants maintained abstinence from illicit opioid use during therapy. Methadone suppresses withdrawal symptoms and reduces opioid craving through its long-acting opioid agonist properties, thereby enhancing treatment stability and decreasing relapse risk (25–27). Timko et al. (25) similarly reported that greater adherence to methadone therapy is associated with lower relapse rates and improved treatment retention.

Two participants exhibited positive urinary morphine concentrations despite enrollment in the MMT program. This outcome may reflect ongoing illicit opioid use potentially associated with psychological stress, environmental influences, inconsistent methadone dosing, or persistent opioid craving. Monroe and Radke reported that withdrawal discomfort and emotional instability are significant contributors to relapse among opioid-dependent individuals receiving substitution therapy (28). Recent studies in addiction medicine have also demonstrated that incomplete adherence to methadone therapy increases the risk of recurrent opioid use and treatment instability.

The observed discrepancy between qualitative strip test results and GC-MS confirmation underscores the necessity of confirmatory toxicological analysis. While three samples initially tested positive with strip tests, only two were confirmed positive by GC-MS, indicating the potential for false-positive results during preliminary screening. Andersen et al. reported that immunoassay-based screening methods offer rapid detection but lower specificity due to possible cross-reactivity with structurally similar compounds (29,30). Consequently, GC-MS is the preferred confirmatory technique because of its superior analytical sensitivity and specificity in detecting opioid compounds and metabolites.

Treatment Adherence Among MMT Patients

The majority of respondents exhibited high levels of treatment adherence, as evidenced by consistent compliance with methadone administration schedules, healthcare appointments, and prescribed therapeutic regimens. High adherence is critical, given that the effectiveness of methadone therapy relies on sustained participation throughout long-term treatment. Pytell reported that patients who maintained stable adherence to methadone therapy experienced improved psychosocial outcomes and reduced opioid dependence (31). Similarly, Cernasev identified family support, accessibility of healthcare services, patient motivation, and effective communication with healthcare providers as key factors influencing adherence (32).

Although high adherence was predominant, a subset of respondents demonstrated moderate or low adherence levels. This observation suggests that sustaining long-term adherence in opioid substitution therapy continues to present significant challenges. Relapse behavior is influenced by multiple factors, including social pressure, insufficient support systems, emotional instability, and persistent cravings. Furthermore, self-reported adherence assessments may underestimate ongoing opioid use due to the tendency of respondents to provide socially desirable answers. Consequently, objective laboratory-based monitoring is necessary to supplement behavioral assessments.

Correlation Between Urinary Morphine Detection and Treatment Adherence

This study identified a statistically significant association between urinary morphine detection and treatment adherence among MMT patients ($p = 0.032$), with a strong correlation strength based on Cramer's V analysis (0.733). These findings support the study hypothesis that better adherence to methadone therapy is associated with lower urinary morphine detection. Similar results were reported by Draghmeh et al (33), who demonstrated that poor adherence contributes to unstable methadone concentrations and increases the risk of relapse and continued opioid use.

Patients with negative urinary morphine results generally exhibited higher adherence scores, while positive urinary morphine findings were more frequently observed among those with lower

adherence. This relationship is clinically significant, as adherence to methadone therapy maintains stable opioid receptor occupancy, suppresses withdrawal symptoms, and reduces illicit opioid consumption. These findings align with previous toxicological studies indicating that urine drug testing serves as an objective biomarker for evaluating compliance in addiction treatment programs (34–36).

The primary contribution of this study is the integration of toxicological confirmation using gas chromatography-mass spectrometry (GC-MS) with behavioral adherence assessment in a primary healthcare-based pharmacotherapy for opioid use disorder (PTRM) setting. Previous research has typically examined either clinical adherence evaluation or laboratory detection in isolation. In contrast, this study combines both methods to offer a more comprehensive assessment of methadone therapy adherence. This integrated approach has the potential to enhance monitoring accuracy and inform evidence-based clinical decision-making in community-based rehabilitation programs.

Clinical Implications of GC-MS Examination

Gas chromatography-mass spectrometry (GC-MS) is widely regarded as the gold standard for opioid confirmation due to its high sensitivity and specificity (37–40). In the present study, GC-MS effectively distinguished true-positive from false-positive screening results, underscoring its critical role in clinical toxicology and rehabilitation monitoring. Recent studies published in 2024 and 2025 further highlight that GC-MS remains among the most reliable confirmatory techniques for detecting opioid metabolites in biological samples, especially within addiction treatment monitoring and forensic toxicology contexts (36,39,41).

Integrating GC-MS examination with adherence assessment offers a more objective monitoring strategy for patients receiving methadone therapy. This combined approach enables healthcare providers to identify relapse risk earlier and to refine individualized intervention strategies. Nevertheless, the routine implementation of GC-MS in healthcare settings is often constrained by operational costs, the need for specialized equipment, and limited laboratory accessibility. As a result, qualitative screening methods remain valuable for preliminary detection, whereas GC-MS should be reserved for confirmatory analysis and treatment evaluation.

CONCLUSION

This cross-sectional study identified a statistically significant association between GC-MS-confirmed urinary morphine detection and methadone treatment adherence among patients receiving Methadone Maintenance Therapy (MMT) at the PTRM Clinic of Gambir Public Health Center. According to the Fisher–Freeman–Halton Exact Test ($p = 0.032$), participants with negative urinary morphine results were predominantly classified as having high treatment adherence, while detectable urinary morphine was observed only among those with moderate or low adherence. These results indicate that urinary morphine testing via GC-MS may offer objective evidence of potential opioid reuse and could complement behavioral and clinical assessments of treatment adherence.

The findings underscore the potential value of integrating toxicological confirmation using GC-MS with conventional adherence assessments to achieve a more comprehensive evaluation of patients undergoing methadone maintenance therapy in primary healthcare settings. Such an integrated approach may enhance clinical monitoring and support the development of robust methadone maintenance services within community-based rehabilitation programs. Further research involving larger sample sizes, multicenter participation, and longitudinal follow-up is recommended to validate these results and clarify the clinical utility of GC-MS-based urinary morphine monitoring in methadone maintenance therapy programs.

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AUTHOR'S CONTRIBUTION STATEMENT

TD: Conceptualization, Methodology, Data Collection, Investigation, Formal Analysis, Writing – Original Draft, Writing – Review & Editing, Funding Acquisition. W: Conceptualization, Methodology, Supervision, Validation, Corresponding Author, Manuscript Review & Editing.

CONFLICT OF INTEREST

None.

DECLARATION OF GENERATIVE AI AND AI-ASSISTED TECHNOLOGIES IN THE WRITING PROCESS

The Authors acknowledge the use of AI-Assisted Technologies to support language improvement, improve clarity, and improve the overall readability and structure of the manuscript.

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DATA AVAILABILITY

The dataset generated and analyzed during the current study is available from the corresponding author upon request.

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