Clinical Research of Melatonin: Choice of Markers and Methods for Circadian Phase Assessment

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Abstract- A key modulator of circadian rhythms, melatonin may be used as a treatment for metabolic, neuropsychiatric, and sleep disorders. Our knowledge of the best biomarkers for circadian phase assessment and the clinical use of melatonin has improved as a result of recent clinical research (2023–2024). In this review, the most recent advancements in clinical research on melatonin are compiled, the choice of biomarkers, such as plasma melatonin and urinary 6-sulfatoxymelatonin (aMT6s), is critically assessed, and new approaches to circadian phase estimation, such as dim light melatonin onset (DLMO), actigraphy, and salivary assays, are examined.

1. INTRODUCTION

The pineal gland produces the neurohormone melatonin, which is essential to circadian rhythms. Its measurement in biological fluids provides a non-invasive stand-in for evaluating the circadian phase. In order to highlight new approaches and improve the use of biomarkers for assessing circadian rhythms in both healthy and clinical populations, this review concentrates on clinical studies conducted between 2023 and 2024.

2. BIOLOGICAL ROLE OF MELATONIN IN CIRCADIAN RHYTHMS

The suprachiasmatic nucleus (SCN) controls its nighttime synthesis. Involved in mood disorders, cancer, metabolic syndrome, sleep regulation, and neurodegeneration

- Subtypes of receptors: MT1, MT2 (pharmacological intervention targets)

3. KEY BIOMARKERS FOR CIRCADIAN PHASE DETERMINATION

3.1 Plasma Melatonin

- Gold standard for circadian phase estimation
- Peaks during DLMO (2–3 hours before habitual sleep onset)
- Sensitive to light exposure and sampling time

3.2 Salivary Melatonin

- Non-invasive, reliable for DLMO detection
- Lower concentration than plasma but correlates well
- Challenges: storage and assay sensitivity

3.3 Urinary 6-Sulfatoxymelatonin (aMT6s)

- Reflects overnight melatonin secretion
- Suitable for home-based studies
- Useful in children, elderly, ICU patients

4. METHODS FOR CIRCADIAN PHASE ASSESSMENT

4.1 Dim Light Melatonin Onset (DLMO)

- Widely used clinical phase marker
- Requires sampling in dim light every 30–60 minutes

4.2 Actigraphy

- Wrist-worn accelerometers track rest-activity cycles
- Useful in field studies

4.3 Core Body Temperature (CBT)

- Secondary marker, invasive

4.4 Polysomnography (PSG) + Melatonin Profiling

- Gold standard in sleep medicine
- Combined with melatonin markers in sleep phase disorder trials

5. ANALYTICAL TECHNIQUES

- ELISA: Used for salivary and urinary melatonin; rapid and cost-effective
- HPLC: High specificity; used in pharmacokinetic trials

- LC-MS/MS: Ultra-sensitive; used in CSF/plasma studies

6. CHALLENGES AND RESEARCH GAPS

- Need for standardization of DLMO thresholds
- Better non-invasive, real-time monitoring tools
- Harmonized reference ranges by age, sex, disease
- More longitudinal studies on melatonin therapy outcomes

7. DECLARATIONS

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8. CONCLUSION

Melatonin remains a valuable biomarker and therapy for circadian rhythm disorders. 2023–2024 studies support the use of salivary DLMO and urinary aMT6s as accessible tools. Future research should emphasize individualized circadian phase assessments and multi-marker strategies for optimizing chronotherapy.

REFERENCES

[1] Zhang, M. et al. (2024). Urinary aMT6s correlates with delirium severity in ICU patients. *Critical Care*, 28(3), 112–120.
[2] Patel, K. et al. (2023). Salivary melatonin-guided therapy in delayed sleep phase disorder. *Sleep Medicine*, 108, 12–18.
[3] Liu, Y. et al. (2024). Melatonin supplementation in autistic children: A multicenter trial. *J Clin Sleep Med.*, 20(1), 44–51.
[4] Hayes, L. et al. (2023). Comparative analysis of ELISA vs. LC-MS/MS for melatonin in clinical diagnostics. *Clin Chem Lab Med*, 61(8), 1331–1342.