

South East London Integrated Medicines Optimisation Committee

Formulary recommendation

Reference:	142
Intervention:	Melatonin modified release (off-label), trazodone, mirtazapine and quetiapine for the pharmacological management of co-morbid insomnia in adults - Melatonin is a naturally occurring hormone produced by the pineal gland and is structurally related to serotonin - Trazodone is a tricyclic-related antidepressant which may have noradrenergic potentiation (exact mechanism of action is not precisely known) - Mirtazapine is an antidepressant which increases central noradrenergic and serotonergic neurotransmission - Quetiapine is an atypical antipsychotic agent with affinity for brain serotonin and dopamine receptors
Date of Decision:	March 2023, updated October 2025 following updates to SEL co-morbid insomnia pathway
Date of Issue:	April 2023, re-issued October 2025
Recommendation:	Amber 2 – initiation and supply by the specialist Sleep Centre at Guy's and St. Thomas' NHS Foundation Trust (GSTfT) until dose is stable and ongoing treatment is indicated only after which prescribing may be transferred to primary care.
Further Information	- Melatonin modified release M/R (off-label), trazodone, mirtazapine and quetiapine are accepted for use in South East London for the pharmacological management of co-morbid insomnia in adults. - Co-morbid insomnia is a sleep disorder believed to arise as a result of another condition such as anxiety, depression, sleep apnoea, gastro-oesophageal reflux disease (GORD), or physical pain - The use of melatonin M/R (off-label), trazodone, mirtazapine and quetiapine for the pharmacological management of co-morbid insomnia in adults should be prescribed in line with the co-morbid insomnia treatment pathway - The initiation of melatonin M/R (off-label), trazodone, mirtazapine and quetiapine is restricted to the specialist Sleep Centre at Guy's and St. Thomas' NHS Foundation Trust team, until a patient's dose is stable and a review determining if ongoing treatment is indicated has occurred. Prescribing can then be continued in primary care under "Amber 2" arrangements. - Cognitive Behaviour Therapy for Insomnia (CBT-I) is recommended as a first line non-pharmacological treatment for co-morbid insomnia in adults where available and appropriate. - Melatonin M/R (licensed indication) and daridorexant are both considered equal first line pharmacological treatment options for patients with chronic insomnia. See the SEL adult Joint Medicines Formulary for further information. - Melatonin M/R (off-label), trazodone, mirtazapine and quetiapine are second line pharmacological treatment options for the management of co-morbid insomnia - Melatonin M/R is recommended off-label in this setting for adults under the age of 55, up to 6mg daily and beyond 13 weeks of treatment. - The use of trazodone, mirtazapine and quetiapine in this setting are also off-label in patients <u>without</u> co-morbid depression. - Informed consent should be gained from the patient before off-label treatment with melatonin M/R, trazodone, mirtazapine and quetiapine is started. - Patients will be reviewed by the specialist sleep centre 3 to 6 months after initiating treatment with melatonin M/R, trazodone, mirtazapine or quetiapine. See the co-morbid insomnia pathway for more information. *Melatonin modified release dose is licensed at 2mg daily for short term treatment of primary insomnia in adults aged 55 or over for up to 13 weeks.
Shared Care/ Transfer of care required:	N/A Practices should be signposted to the co-morbid insomnia pathway

Cost Impact for agreed patient group	The following cost impact is based on assumptions that 35% of the total patients from the sleep centre are from SEL and that treatment is long term: • Melatonin M/R: Based on an average of 4mg daily and approximately 720 patients per annum eligible for treatment, estimated costs for SEL are £95,000 per annum (~£5,000 per 100,000 population) • Trazodone: Based on approximately 150 patients per annum eligible for treatment, estimated costs for SEL are £2,000 per annum (~£105 per 100,000 population) • Mirtazapine: Based on approximately 150 patients per annum eligible for treatment, estimated costs for SEL are £1,000 per annum (~£53 per 100,000 population) • Quetiapine: Based on approximately 50 patients per annum eligible for treatment, estimated costs for SEL are £350 per annum (~£19 per 100,000 population) However, it is likely that the majority of the estimated costs are already in baseline as several of these treatments, including melatonin, are likely to be in routine practice for the use in co-morbid insomnia.
Usage Monitoring & Impact Assessment	Acute Trusts: Monitor and audit usage of melatonin M/R, trazodone, mirtazapine and quetiapine as agreed and report back to the Committee (against this recommendation) upon request of the Committee SEL Borough Medicines Teams • Monitor ePACT2 data and exception reports from GPs if inappropriate prescribing requests are made to primary care
Evidence reviewed	References (from evidence review): 1. Sateia M, Buysse D, Krystal A et al. Clinical Practice Guideline for the Pharmacologic treatment of Chronic Insomnia in Adults: An American Academy of Sleep Medicine Clinical Practice Guideline. Clinical practice guideline for the pharmacologic treatment of chronic insomnia in adults: An American Academy of sleep medicine clinical practice guideline. J Clin Sleep Med 13: 307–349. 2. CKS. Insomnia. Available here [Accessed 25/06/2021] 3. Insomnia, KTT6, September 2019. Available here [Accessed 25/06/2021] 4. Riemann D, Baglioni C, Bassetti C, et al. (2017) European guideline for the diagnosis and treatment of insomnia. J Sleep Res 26: 675–700. 5. Mirtazapine. Summary of Product Characteristics. Available here [Accessed 25/06/2021] 6. Savarese M, Carnicelli M, Cardinali V, et al. (2015) Subjective hypnotic efficacy of trazodone and mirtazapine in patients with chronic insomnia: A retrospective, comparative study. Arch Ital Biol 153: 243–250. 7. Karsten J, Hagenauw LA, Kamphuis J, et al. (2017) Low doses of mirtazapine or quetiapine for transient insomnia: A randomised, double-blind, cross-over, placebo-controlled trial. J Psychopharmacol 31: 327–337. 8. Aslan S, Isik E and Cosar B (2002) The effects of mirtazapine on sleep: A placebo controlled, double-blind study in young healthy volunteers. Sleep 25: 666–668. 9. Ruwe F, P IJ-B, Roth T, et al. (2016) A phase 2 randomized dose-finding study with esmirtazapine in patients with primary insomnia. J Clin Psychopharmacol 36: 457–464 10. Ivy-May N, Roth T, Ruwe F, et al. (2015) Esmirtazapine in non-elderly adult patients with primary insomnia: Efficacy and safety from a 2-week randomized outpatient trial. Sleep Med 16: 831–837 11. Trazodone Stat Pearls. Available online here [Accessed 26/06/2021] 12. Trazodone. Summary of Product Characteristics. Available here [Accessed 26/06/2021] 13. Everitt H, Baldwin DS, Stuart B. Antidepressants for insomnia in adults (review). Cochrane Database of Systematic Reviews 2018. 14. Yi X, Ni S, Ghadami M et al. Trazodone for the treatment of insomnia: a meta-analysis of randomized placebo controlled Trials. Sleep Medicine 2018 DOI 10.1016/j.sleep.2018.01.010 15. Roth AJ, McCall WV, Liguori A. Cognitive, psychomotor and polysomnographic effects of trazodone in primary insomniacs. J Sleep Res 2011;20 p552-558. 16. Walsh JK, Erman M, Erwin CW, et al. Subjective hypnotic efficacy of trazodone and zolpidem in DSMIII-R primary insomnia. Hum Psychopharmacol 1998 (13) p191-198. 17. Andersen S, Vande Griend J. Quetiapine for insomnia: A review of the literature. Am J HealthSyst Pharm—Vol 71 Mar 1, 2014 p394-402. 18. Kamphuis J, Taxis K, Schuiling-Veninga C et al. Off-Label Prescriptions of Low-Dose Quetiapine and Mirtazapine for Insomnia in The Netherlands. Journal of Clinical Psychopharmacology Volume 35, Number 4, August 2015 p468-470. 19. Bertisch SM, Herzig SJ, Winkelman JW, et al. (2014) National use of prescription medications for insomnia: NHANES 1999–2010. Sleep 37: 343–349. 20. Seroquel (quetiapine). Summary of Product Characteristics. Available here [Accessed 27/06/2021] 21. Wiegand MH, Landry F, Bruckner T, et al. (2008) Quetiapine in primary insomnia: A pilot study. Psychopharmacology 196: 337–338. 22. Tassniyom K, Paholpak S, Tassniyom S, et al. (2010) Quetiapine for primary insomnia: A double blind, randomized controlled trial. J Med Assoc Thai 93: 729–734. 23. Mi W, Tabarak S, Wang L et al. Effects of agomelatine and mirtazapine on sleep disturbances in major depressive disorder: evidence from polysomnographic and resting-state functional connectivity analyses. Sleep 2020 doi: 10.1093/sleep/zsaa092. 24. Circadin (Melatonin) SR tablets. Summary of Product Characteristics. Available here [Accessed 19/07/2021] 25. Low T, Choo F, Tan S et al. The efficacy of melatonin agonists in insomnia – an umbrella review. Journal of Psychiatric Research 2020 121 p10-23. 26. Rios P, Cardoso R, Morra D et al. Comparative effectiveness and safety of pharmacological and non-pharmacological interventions for insomnia: an overview of reviews. Systematic Reviews 2019 8:281 27. Lemoine P, Garfinkel D, Laudon M, et al. Prolonged-release melatonin for insomnia: an openlabel long-term study of efficacy, safety, and withdrawal. Ther Clin Risk Manag. 2011;7:301–11. 28. Wade AG, Ford I, Crawford G, et al. Efficacy of prolonged release melatonin in insomnia patients aged 55–80 years: quality of sleep and next-day alertness outcomes. Curr Med Res Opin. 2007;23(10):2597–605.

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| | <p>29. Wade AG, Crawford G, Ford I, et al. Prolonged release melatonin in the treatment of primary insomnia: evaluation of the age cut-off for short- and long-term response. <i>Curr Med Res Opin.</i> 2011;27(1):87–98.</p> <p>30. Li, T., Jiang, S., Han, M., Yang, Z., Lv, J., Deng, C., Reiter, R.J., Yang, Y., 2018. Exogenous melatonin as a treatment for secondary sleep disorders: a systematic review and meta-analysis. <i>Front. Neuroendocrinol.</i> https://doi.org/10.1016/j.yfrne.2018.06.</p> <p>31. Buscemi, N., Vandermeer, B., Hooton, N., Pandya, R., Tjosvold, L., Hartling, L., Baker, G., Klassen, T.P., Vohra, S., 2005. The efficacy and safety of exogenous melatonin for primary sleep disorders: a meta-analysis. <i>J. Gen. Intern. Med.</i> https://doi.org/10.1111/j.1525-1497.2005.0243.</p> |
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NOTES:

- a) SEL IMOC recommendations and minutes are available via the [website](#)
- b) This SEL IMOC recommendation has been made on the cost effectiveness, patient outcome and safety data available at the time. The recommendation will be subject to review if new data becomes available, costs are higher than expected or new NICE guidelines or technology appraisals are issued.
- c) **Not to be used for commercial or marketing purposes. Strictly for use within the NHS.**