Pathway for the pharmacological management of co-morbid insomnia in adults

This pathway is mainly intended for use in secondary care. However, acute insomnia and chronic insomnia can be managed in primary care in line with this pathway.

Note: Melatonin, trazodone, mirtazapine and quetiapine are IMOC Amber 2 category – initiation by the sleep centre followed by maintenance prescribing in primary care. GPs are not expected to initiate these treatments but may be asked to take on prescribing in line with IMOC recommendations.
Doxepin, agomelatine and vortioxetine are IMOC RED category (hospital only) – initiation and ongoing prescribing will be by the sleep service.

Please review this flowchart in conjunction with the supporting information on the next page

Initial assessment and management

Screen for associated perpetuating factors and optimise management accordingly (e.g. pain, acid reflux, depression, anxiety).

- Optimise lifestyle factors, such as exercise and sleep routine
- Offer CBT-I or digital CBT-I before pharmacological treatment where available and appropriate.
- CBT-I may be repeated/added in any step of pathway Patient choice should be considered. *For detail on CBT-I, see appendix 2*

For Acute Insomnia[1]

Only for consideration for transient or expected short-term comorbid insomnia

First line pharmacological therapy

Zopiclone 3.75 mg to 7.5 mg at night

Zolpidem 5 mg to 10 mg at night

>2 weeks use not recommended outside of Sleep Centre patient assessment

For Chronic Insomnia[1]

First line pharmacological therapy

Consider melatonin M/R 2mg at night (over 55s) for 13 weeks max **OR** daridorexant 25mg to 50mg at night[2,3]. Where treatment is ineffective, trial the alternative first-line treatment option

Please note the following:
Green box = management in primary or secondary care **Red box** = referral into secondary care required

Second line pharmacological therapy options (*off label use*)

- Melatonin M/R tablets 2mg at night (take 1-2 hours before bedtime), increasing up to 6mg if required4
- Trazodone 50 mg to 150 mg at night[5 6]
- Mirtazapine 7.5 mg to 15 mg at night[6]

Use permitted only after Sleep Disorder Centre MDT discussion

- Quetiapine 12.5 mg to 50 mg at night[6]
- Trazodone 150 mg to 300 mg at night[5 8]
- Doxepin 3 mg to 10 mg at night[7] *(RED - hospital only)*
- Agomelatine 25 mg to 50 mg at night[5 8] *(RED - hospital only)*
- Vortioxetine 5 mg titrated up to 20mg in the morning[8] *(RED - hospital only)*

General principles of patient management in the Sleep Disorder Centre

- Patients are reviewed by the specialist 3 to 6 months after starting a treatment.
  - *Aim for a reduction of >6 in the ISI (Insomnia Severity Index)*
  - InsomniaIndex (ons.org)
  - *Aim for HADs score of <10 (no validated reduction in this scale)*
    Depression and anxiety self-assessment quiz - NHS (www.nhs.uk)
- Patients on red listed drugs will remain under the care of the sleep service
- Patients are counselled on initiation, including when to dose titrate, and when to stop treatment if not working or no longer necessary. This detail is clearly communicated to GPs in the clinic letter.
- Provided the patient's dose is stable and ongoing treatment is indicated, primary care prescribing may be requested after initial supplies from the clinic.
- When CBT-I principles are embedded with/without pharmacological treatment and insomnia resolved, the treatment may be deprescribed- the GP will be informed via a clinic letter, including detail of treatment tapering

South East London Integrated Medicines Optimisation Committee (SEL IMOC). A partnership between NHS organisations in South East London Integrated Care System: SEL Integrated Care Board (covering the boroughs of Bexley/Bromley/Greenwich/ Lambeth/Lewisham and Southwark) and GSTFT/KCH /SLaM/ Oxleas NHS Foundation Trusts and Lewisham & Greenwich NHS Trust

Pathway for the pharmacological management of co-morbid insomnia in adults

This pathway is mainly intended for use in secondary care. However, acute insomnia and chronic insomnia can be managed in primary care in line with this pathway.

Note: Melatonin, trazodone, mirtazapine and quetiapine are IMOC Amber 2 category – initiation by the sleep centre followed by maintenance prescribing in primary care. GPs are not expected to initiate these treatments but may be asked to take on prescribing in line with IMOC recommendations.
Doxepin, agomelatine and vortioxetine are IMOC RED category (hospital only) – initiation and ongoing prescribing will be by the sleep service.

Key for Supportive information:

[1] Chronic insomnia can be diagnosed if symptoms occur on at least 3 nights per week for 3 months or more. Short-term insomnia can be diagnosed if symptoms have been present for less than 3 months.

[2]CBT for insomnia (CBTi) remains the first-line treatment for insomnia disorder. Daridorexant may provide an efficacious option for patients as a second-line treatment option when digital or face-to-face CBTi has been tried but not worked, or as a first-line treatment option when CBTi is not available or unsuitable in adults with symptoms lasting for 3 nights or more per week for at least 3 months, and whose daytime functioning is considerably affected , as recommended by NICE.
[3] Daridorexant is a Green categorised medication. A lower dose of 25mg dose at night may be prescribed with close monitoring, for patients with moderate hepatic impairment (LFTs taken 6-12 months) or in elderly patients or those at risk of falls (GP to periodically assess frailty index considering other risk factors for falls).

[4] Melatonin should be avoided in chronic insomnia associated with nightmare disorders in adults with post-traumatic stress disorder (PTSD). For the management of chronic insomnia associated with nightmare disorders in PTSD, trazodone may be used as 1st line pharmacological treatment (to be discussed in MDT). If trazodone is ineffective or not tolerated then stop treatment and consider starting agomelatine (2nd line pharmacological treatment in this setting). See the management of nightmare disorders in adult patients PTSD for further information.

[5] Trazodone and agomelatine dose for insomnia without co-morbid nightmares associated with PTSD. See the management of nightmare disorders in adult patients PTSD for trazodone and agomelatine dosing information in adults with chronic insomnia associated with nightmare disorders in PTSD.

[6]Use in patients without comorbid depression is off-label

[7]Off-label Hospital prescribing only.

[8]Used only in patients with insomnia comorbid with depression, so can be considered within product license. Hospital prescribing only. For detail, see appendix 3

Appendix 1 – Understanding the condition

Sleep Foundation

Sleeping problems often have a bidirectional relationship with other health issues.

Co-morbid insomnia is a sleep disorder believed to arise as a result of another condition such as anxiety, depression, sleep apnoea, gastroesophageal reflux disease (GERD), or physical pain.

Acute Insomnia

Acute insomnia otherwise know as short-term insomnia is a brief episode of difficulty sleeping.
It may be caused by a stressful life event such as a bereavement, global pandemic or a major job or relationship change.
Acute insomnia tends to last for less than three months. However, it can be persistent and become chronic insomnia.

Chronic Insomnia

Chronic insomnia is a long-term pattern of difficulty sleeping.
Insomnia is considered chronic if a person has trouble falling asleep or staying asleep at least three nights per week for three months or longer. Like acute insomnia, it may be linked to stressful situations, but it may also be related to irregular sleep schedules, poor sleep hygiene, other sleep disorders etc.

Appendix 2 – Non-pharmacological Management

Cognitive Behavioral Therapy for Insomnia (CBT-I)

CBTi is an evidence-based therapy developed specifically for patients with Insomnia. CBT-I is recommended as the first-line treatment of both acute and long-term insomnia in adults.

CBTI targets the underlying causes of insomnia, and provides patients with a set of skills for managing their sleep. It is a good treatment choice if patients have had long-term sleeping problems, are concerned about becoming dependent on sleep medications, or have found medication ineffective or limited by undesirable side effects.

Lifestyle optimisation measures

- Stimulus control
  - Bed/bedroom use only for sleep, sex and getting dressed (not reading, resting, phone, watching TV etc.)
  - Get out of bed if not sleeping after 15-20 min (especially if agitated)

- Sleep scheduling
  - Limit time in bed to time actual average total sleep time (best achieved via sleep diaries)
  - Avoiding daytime and evening naps
  - Getting into bed only when sleepy tired
  - Getting up at the same time every day, including weekends

- Additional
  - Avoid caffeine after 12pm; switch to decaffeinated drinks
  - Avoid alcohol, at the very least in the 2 hours before bed
  - Daily exercise, ideally outside to gain exposure to natural day light
  - Other sleep hygiene advice via the Sleep Foundation

- Naps
  - Discouraged because they reduce sleep drive.
  - If naps cannot be avoided, then try to limit them to 20 minutes (setting an alarm), and ideally not in the 5 hours before the main episode of sleep.

- Digital CBT-I available
  - Sleepio - Currently available free in some areas in the UK)
  - Sleepstation – Available free on the NHS. The patient self-refers and then sees the GP who needs to approve the referral

Recommended resources for CBT-I

- Overcoming Insomnia: A Cognitive-Behavioural Therapy Approach, Workbook (Treatments That Work) by Jack Edinger & Colleen Carney (2014)
- Overcoming Insomnia and Sleep Problems: A Self Help Guide Using Cognitive Behavioural Techniques by Colin Espie (2012)
- Say Goodnight to Insomnia: A Drug-Free Programme Developed at Harvard Medical School by Gregg Jacobs (2011)
- How to Beat Insomnia and Sleep Problems One Step at a Time: Using evidence-based low- intensity CBT by Kirstie Anderson (2018)

Pathway for the pharmacological management of co-morbid insomnia in adults

This pathway is mainly intended for use in secondary care. However, acute insomnia and chronic insomnia can be managed in primary care in line with this pathway.

Note: Melatonin, trazodone, mirtazapine and quetiapine are IMOC Amber 2 category – initiation by the sleep centre followed by maintenance prescribing in primary care. GPs are not expected to initiate these treatments but may be asked to take on prescribing in line with IMOC recommendations.
Doxepin, agomelatine and vortioxetine are IMOC RED category (hospital only) – initiation and ongoing prescribing will be by the sleep service.

Appendix 3
Patient cohorts appropriate for second line pharmacological therapies used in the management of co-morbid insomnia

- SEL IMOC formulary recommendations for melatonin modified release, trazodone, mirtazapine and quetiapine for the pharmacological management of co-morbid insomnia in adults can be accessed here.
- SEL Integrated Medicines Optimisation Committee Formulary recommendation for doxepin, agomelatine and vortioxetine for the pharmacological management of co-morbid insomnia in adults can be accessed here
- The SEL Joint Formulary entries for the below tabled medications can be accessed here.

Drug	Types of patients this is most useful for	Cautions
Melatonin	• Sleep initiation and maintenance difficulties • Co-morbid REM Sleep Behavioural Disorder and/or NREM parasomnia	• As melatonin increases the time in REM, it should be avoided in chronic insomnia associated with nightmare disorders in adults with post-traumatic stress disorder (PTSD) • Avoid in patients with unstable epilepsy
Trazodone	• Sleep initiation and maintenance difficulties • Co-morbid nightmares • Co-morbid Restless Legs Syndrome	• History of impulsive drug overdose • Prolonged QTc interval
Mirtazapine	• Sleep initiation and maintenance difficulties. • Co-morbid prominent nocturnal anxiety	• Not helpful in nightmares • Can worsen restless legs syndrome
Quetiapine	• Severe insomnia, which has not responded to trazodone nor mirtazapine • Paradoxical insomnia	• Prolonged QTc interval • Can use with other anti-psychotics in dose range for insomnia; total antipsychotic dose load to be calculated
Doxepin	• Sleep initiation and maintenance difficulties. • When a liquid hypnotic is required e.g. PEG fed etc. • In patients with intellectual disabilities • In patients where there is no response to trazodone or mirtazapine, or where these are contraindicated	• Patient or carer needs to be able to make new doxepin solution each evening. • For administration: i. Dissolve and stir the contents of one 25mg capsule into 25mls of water to make a 1mg/ml solution ii. For a 3mg dose take 3mls of this solution 30 minutes before bed iii. The dose may be increased in weekly 1ml (i.e. 1mg) increments to a maximum of 10mls (i.e. 10mg) depending on tolerability and efficacy.
Agomelatine	• Insomnia with co-morbid depression. • If treatment failure on melatonin for REM Sleep Behavioural Disorder. • Consider in Smith Magenis Syndrome if lack of response to melatonin	• Not in patients with hepatic dysfunction.
Vortioxetine	• Depression with insomnia • Depression with REM Sleep Behavioural Disorder • Depression with sleep movement disorders	