Opioid Agonist Therapy 101: An Introduction to Clinical Practice

Initiation & Maintenance

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- **<u>Potential for conflict(s) of interest</u>:**
  - None identified

Declaration of off-label medication recommendations

- **During this presentation, I will make therapeutic recommendations for medications that have not received regulatory approval (i.e. off-label use of medication). I will verbally identify each off-label recommendations prior to discussing it.**

Faculty/Presenter Disclosure

- **Faculty:** Dr. Erin Knight

- **Relationships with commercial interests:**
- **None**

Learning Objectives

Upon completion of this session the participant should have an understanding of the management of important issues in the maintenance phase of treatment including

- Initiating and dose adjustments
  - buprenorphine/naloxone: classic and microdosing starts
  - extended release buprenorphine
  - methadone
- Managing 'carry' doses
  - buprenorphine/naloxone
  - methadone
- Managing missed doses
  - buprenorphine/naloxone
  - methadone
- Managing vomited doses
- Using, interpreting and responding to urine drug screens
- Managing concurrent substance use
- Treatment of insomnia

MANITOBA BUPRENORPHINE/NALOXONE RECOMMENDED PRACTICE MANUAL

The College convened a working group of experts in the treatment of opioid use disorder in the spring of 2019. This working group has been tasked with assisting College staff in developing a new Recommended Practice Manual for the use of buprenorphine/naloxone in the context of Opioid Agonist Therapy in Manitoba. The College receives frequent requests for guidance on the issues the working group is discussing. The working group has thus elected to publish its recommendations, in the areas of care that generate the most frequent inquiries, below.

Physicians are encouraged to adopt and incorporate these recommendations into their Opioid Agonist Therapy practices without delay. Please note that once the work of the working group is concluded, the complete new manual will be made available online on the College website. Should members have any questions about the interpretation of the guidance published in the documents below in the interim, please do not hesitate to contact the chair of the working group, Dr. Marina Reinecke at the CPSM. It is the working group's hope that you will find this guidance useful in providing care to your patients on buprenorphine/naloxone.

- Buprenorphine/naloxone Take-home (Carry) Dosing Recommendations
- Unwitnessed Induction Section
- In-Hospital Care Section
- Micro-dosing Guidance

- http://cpsm.mb.ca/prescribing-practices-program/manitoba-buprenorphine-naloxone-recommended-practice-manual

Initiating – buprenorphine/naloxone - classic start

- Patient must be in moderate withdrawal (if recent opioid use)
  - Minimum 4-8 hours since last short acting opioid, 24+ hours since last long-acting
  - Assess using COWS: score >= 12 prior to starting
- Day 1 initial dose: 2-8 mg depending on withdrawal severity and opioid tolerance
  - 2-4 mg top-up doses q1h PRN
  - typical outpatient max dose day 1 = 12-16mg
  - consider higher doses if previously on high dose buprenorphine, high opioid tolerance
- Day 2-3 initial dose: total of previous day ± additional 2-4 mg
  - A second dose can be given after 2-4 hours
- Dose can be adjusted daily
  - A stable dose can be reached within 1-4 days

See Handout

APPENDIX 1
Clinical Opiate Withdrawal Scale

For each item, circle the number that best describes the patient's signs or symptom. Rate on just the apparent relationship to opiate withdrawal. For example, if heart rate is increased because the patient was jogging just prior to assessment, the increase pulse rate would not add to the score.

Patient's Name:_____ Date and Time ____/____/____:_____

Reason for this assessment:_____

Resting Pulse Rate: _____beats/minute *Measured after patient is sitting or lying for one minute* 0 pulse rate 80 or below 1 pulse rate 81-100 2 pulse rate 101-120 4 pulse rate greater than 120	**GI Upset**: *over last 1/2 hour* 0 no GI symptoms 1 stomach cramps 2 nausea or loose stool 3 vomiting or diarrhea 5 multiple episodes of diarrhea or vomiting
Sweating: *over past 1/2 hour not accounted for by room temperature or patient activity.* 0 no report of chills or flushing 1 subjective report of chills or flushing 2 flushed or observable moistness on face 3 beads of sweat on brow or face 4 sweat streaming off face	**Tremor** *observation of outstretched hands* 0 no tremor 1 tremor can be felt, but not observed 2 slight tremor observable 4 gross tremor or muscle twitching
Restlessness *Observation during assessment* 0 able to sit still 1 reports difficulty sitting still, but is able to do so 3 frequent shifting or extraneous movements of legs/arms 5 unable to sit still for more than a few seconds	**Yawning** *Observation during assessment* 0 no yawning 1 yawning once or twice during assessment 2 yawning three or more times during assessment 4 yawning several times/minute
Pupil size 0 pupils pinned or normal size for room light 1 pupils possibly larger than normal for room light 2 pupils moderately dilated 5 pupils so dilated that only the rim of the iris is visible	**Anxiety or Irritability** 0 none 1 patient reports increasing irritability or anxiousness 2 patient obviously irritable or anxious 4 patient so irritable or anxious that participation in the assessment is difficult
Bone or Joint aches *If patient was having pain previously, only the additional component attributed to opiates withdrawal is scored* 0 not present 1 mild diffuse discomfort 2 patient reports severe diffuse aching of joints/muscles 4 patient is rubbing joints or muscles and is unable to sit still because of discomfort	**Gooseflesh skin** 0 skin is smooth 3 piloerrection of skin can be felt or hairs standing up on arms 5 prominent piloerrection
Runny nose or tearing *Not accounted for by cold symptoms or allergies* 0 not present 1 nasal stuffiness or unusually moist eyes 2 nose running or tearing 4 nose constantly running or tears streaming down cheeks	Total Score _____ The total score is the sum of all 11 items Initials of person completing assessment: _____

Score: 5-12 = mild; 13-24 = moderate; 25-36 = moderately severe; more than 36 = severe withdrawal

This version may be copied and used clinically.

Source: Wesson, D. R., & Ling, W. (2003). The Clinical Opiate Withdrawal Scale (COWS). *J Psychoactive Drugs*, 35(2), 253–9.

Initiating – buprenorphine/naloxone - an alternate approach: microdosing

Substance Abuse and Rehabilitation

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CASE SERIES

Use of microdoses for induction of buprenorphine treatment with overlapping full opioid agonist use: the Bernese method

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Substance Abuse and Rehabilitation
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Number of times this article has been viewed

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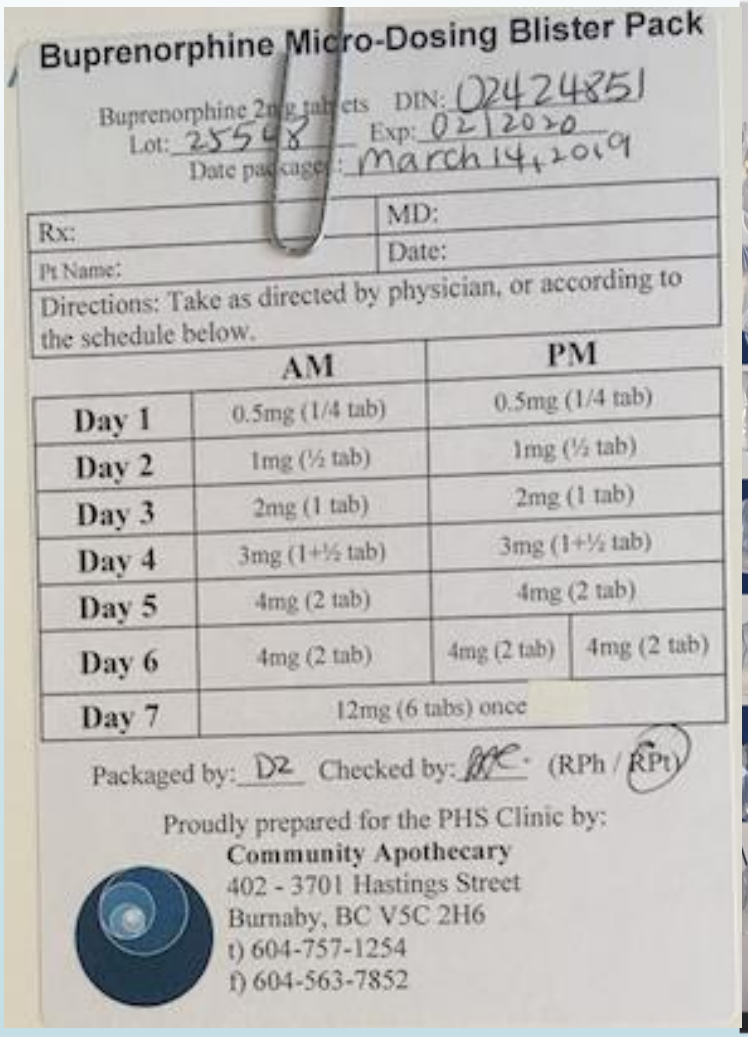
Background: Buprenorphine is a partial μ-opioid receptor agonist used for maintenance treatment of opioid dependence. Because of the partial agonism and high receptor affinity, it may precipitate withdrawal symptoms during induction in persons on full μ-opioid receptor agonists. Therefore, current guidelines and drug labels recommend leaving a sufficient time period since the last full agonist use, waiting for clear and objective withdrawal symptoms, and reducing pre-existing full agonist therapies before administering buprenorphine. However, even with these precautions, for many patients the induction of buprenorphine is a difficult experience, due to withdrawal symptoms. Furthermore, tapering of the full agonist bears the risk of relapse to illicit opioid use.

Initiating – buprenorphine/naloxone - an alternate approach: microdosing



Buprenorphine Micro-Dosing Blister Pack

Buprenorphine 2mg tablets DIN: 02424851
Lot: 25548 Exp: 02/2020
Date packaged: March 14, 2019

Rx:	MD:
Pt Name:	Date:
Directions: Take as directed by physician, or according to the schedule below.	

	AM	PM	
Day 1	0.5mg (1/4 tab)	0.5mg (1/4 tab)	
Day 2	1mg (½ tab)	1mg (½ tab)	
Day 3	2mg (1 tab)	2mg (1 tab)	
Day 4	3mg (1+½ tab)	3mg (1+½ tab)	
Day 5	4mg (2 tab)	4mg (2 tab)	
Day 6	4mg (2 tab)	4mg (2 tab)	4mg (2 tab)
Day 7	12mg (6 tabs) once		

Packaged by: D2 Checked by: MC (RPh / RPt)

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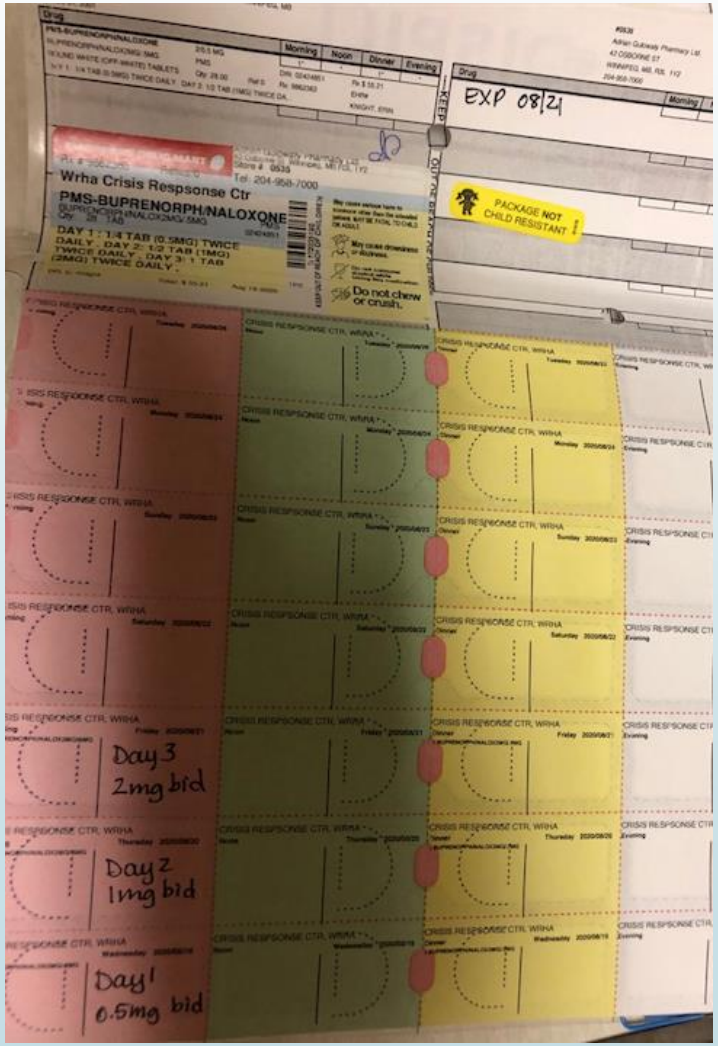
Initiating – buprenorphine/naloxone - an alternate approach: microdosing



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Rapid Micro-Induction of Buprenorphine/Naloxone for Opioid Use Disorder in an Inpatient Setting: A Case Series

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TABLE 1. Titration schedule for Case 1

	Buprenorphine/Naloxone*		Hydromorphone	
	Dosing	Total Daily Dose	Dosing	Total Daily Dose
Day 0	N/A		1-4 mg IV q4h PRN	3 mg
Day 1	0.25g SL q4h	1 mg	1-4 mg IV q4h PRN	11 mg
Day 2	0.5 mg SL q4h	2.5 mg	1-4 mg IV q4h PRN	15 mg
Day 3	1 mg SL q4h	5 mg	1-4 mg IV q4h PRN	15 mg
Day 4	2 mg SL q4h	8 mg	1-4 mg IV q4h PRN	4 mg
Day 5	16 mg SL daily	16 mg	Discontinued	

*Expressed as milligrams of buprenorphine in buprenorphine/naloxone sublingual tablet.

	Buprenorphine/Naloxone*		Hydromorphone	
	Dosing	Total Daily Dose	Dosing	Total Daily Dose
Day 0	N/A		3 mg PO q4h regular 2-4 mg PO q4h PRN	24 mg
Day 1	0.5 mg SL q3h	2.5 mg	3 mg PO q4h regular 2-4 mg PO q4h PRN	26 mg
Day 2	1 mg SL q3h	8 mg	3 mg PO q4h regular 2-4 mg PO q4h PRN	24 mg
Day 3	12 mg SL daily	12 mg	Discontinued	

*Expressed as milligrams of buprenorphine in buprenorphine/naloxone sublingual tablet.

Dose Adjustments – buprenorphine/naloxone

- As dose increases, duration without withdrawal increases & cravings decrease
- Balance prevention of withdrawal, cravings and illicit use vs. avoidance of side-effects
  - Avoid dose increases for seeking sedative effect, treated co-occurring disorders (ex. anxiety, PTSD, chronic pain)
- Usual dose: 8-24mg
- After initial induction, allow 3-7 days between dose increases
- Stability achieved much more quickly than with methadone, often within 1 week
- Doses > 24 mg are sometimes needed, up to 32mg

Extended release buprenorphine – initiation and dose adjustments

- Probuphine 80mg subdermal implants
  - Stabilize on 8mg or less for the past 90 days
  - No dose adjustments after implantation
  - Implants to be changed q6 months
- Sublocade 100 & 300mg subcut injections
  - Stabilize on 8-24mg for 7 days
  - First 2 doses 300mg, then 100mg monthly
    - Consider "top-up" with SL buprenorphine in first 2 months if ongoing withdrawal
  - If cravings/withdrawal/use on 100mg monthly, can increase to 300mg ongoing
  - Injections anytime between 26-42 days
    - if > 42 days, restart on SL buprenorphine

Initiating – methadone

Start LOW & Go SLOW - first 3-5 days

Opioid tolerance	Methadone starting dose
Low, including recent abstinence	10mg or less
Moderate, or high but risk factors for methadone toxicity	20mg or less
High, no risk factors for methadone toxicity	30mg or less

Max starting dose is 30mg

Dose Adjustments – methadone *new*

The initial dose should be 10-30 mg of methadone per day for at least the first three days. Patients at high-risk for methadone toxicity should start on no more than 10-20 mg.

During the early stabilization phase for patients new to methadone, doses may be increased by up to 5 mg every 3-5 days, or by 10 mg increments every 7 or more days.

During the early stabilization phase for patients new to methadone, you may elect to prescribe a single dose increase of 10 mg after 5 days, but all subsequent 10 mg dose increases should occur no sooner than 7 days apart. Alternatively, a 5mg dose increase may be considered 5 days after a 10 mg dose increase. **Caution surrounding serial 10 mg dose increases is emphasized.**

Initiating – methadone

Start LOW & Go SLOW – The First 2 Weeks

- Assess for dose increases once or twice weekly
  - 5-10 mg q 3 to 7 days
  - If recent abstinence or high risk of toxicity: increase by 5mg or less q 5-7 days
- The highest risk for overdose is in the first 2 weeks on methadone
  - 6.7x higher risk of OD than the heroin addict NOT in treatment
- The goal is to reach a dose which lasts 24 hours
- Much longer titration to target dose than with buprenorphine/naloxone

Dose Adjustments – methadone

- *As dose increases, duration without withdrawal increases & cravings decrease*
- *Balance prevention of withdrawal, cravings & illicit use vs. avoidance of side-effects*
  - *Avoid dose increases for seeking sedative effect, treated co-occurring disorders (ex. anxiety, PTSD, chronic pain)*
- Usual dose: 60-120mg
- Initially, increase dose by 5-10mg Q 3-7 days
- As the dose effect gets closer to lasting 24 hours, or over 60 mg, slow down the dose increases to 3-5mg Q 5-7 days
- Doses > 120mg are sometimes needed
  - ECG to check QTc
  - Consider peak: trough
- Peak: trough > 2 = rapid metabolizer
  - may be idiopathic or medication related: ARVs, dilantin, rifampin
  - Consider split dose

Managing "carry" doses – buprenorphine/naloxone

- **Buprenorphine is NOT methadone** – safety profile much better = carries are safer and more flexible
- General principles
  - Daily witnessed dosing until clinical stability demonstrated
    - Stable dose, infrequent missed doses, UDS supportive, regular follow-up, safe storage
  - Weigh benefits of more flexible dosing vs. risks of diversion
- Most common scenario:
  - one additional carry dose every 2 weeks until weekly dispense
  - After further 3 months stability, transition to q2 week dispense
  - After 1 year stability, transition to monthly dispense
- Exceptions to progress quicker are possible, based on clinical judgment
- Reassess continually, if destabilization occurs, increase frequency of dispensing

Managing "carry" doses - methadone

- All patients start with daily witnessed dosing
- Take - home doses can be given when
  - At least 2 months in treatment
  - *Clinical Stability* is demonstrated
    - Dose stable, UDS consistent with substance use disorders in remission
    - Psychosocial stability (emotional, psychological, housing, family life…)
    - Adhering to treatment agreement, attending follow-ups…
  - Client is able to store medication safely in a locked box
  - Increased by 1 carry dose every 3-4 weeks, up to maximum 6 carries/week
- Continual reassessment
- Must consider patient safety & public safety when deciding to give carries

Managing missed doses – buprenorphine/naloxone

- Missed doses can indicate a variety of problems including relapse to substance use or social instability
  - assess for stability
  - explore reasons for missed doses
- Pharmacists report missed doses to the physician or clinic daily
- Due to the partial agonist effect & lower risk of overdose, dose adjustment after missed doses does not require the same degree of vigilance as with methadone
- 5 consecutive missed doses = Rx cancelled
  - Patient should be assessed & dose should be reduced to (ex. 50% of previous dose or 8 mg)
    - if using other opioids, assess COWS to avoid precipitated withdrawal with restart
- 6 or more missed doses – reassess & restart induction process

Managing missed doses – methadone

- Missed doses can indicate a variety of problems including relapse to substance use or social instability
  - assess for stability
  - explore reasons for missed doses
- Pharmacists report missed doses to the physician or clinic daily
- 3 or more consecutive missed doses = Rx cancelled
  - Loss of tolerance in as little as 3 days
  - Doses < 30mg
    - After reassessment, can either continue at same dose or reduce dose
  - Doses > 30mg
    - Decrease by 50% or to starting dose (ex. 30mg), whichever is higher
    - If daily assessment possible, may increase by up to 5-10mg daily
    - If daily assessment not possible, or if unstable or using other sedatives, increase dose more slowly
- 4 or more missed doses = reassess and restart

Managing vomited doses

- No replacement unless the emesis is directly witnessed by a professional
  - Exception might be in pregnancy
- If vomiting within 15 min. consider replacing 50-75% of the dose
- If vomiting within15–30 min. consider replacing 25-50% of dose
- Consider pre-treated for nausea prior to replacement
- Observe for further nausea & for sedation for at least 30 min. after replacement dose

Using, interpreting and responding to urine drug screens

- Why?
  - Corroborates history provided by the client
    - At admission to document opioid use
    - During stabilization to monitor progress
    - During maintenance to monitor stability and facilitate carry doses
  - Confirms stability or identifies relapse
- How?
  - Random UDS preferred
  - Measures to prevent tampering
    - Leave bags, bulky clothes, empty pockets
    - Bathroom with 'blued' toilet, no access to warm tap water
    - Temperature strip on bottle
  - Point of care VS. lab-based immunoassay VS. GC-MS (comprehensive)

Using, **interpreting** and responding to urine drug screens

- What we're looking for
  - Methadone (MTD) & methadone metabolites (EDDP)
    - To ensure it's there, (particularly if carry doses)
  - Opioids (MOP, OXY, FEN)
    - To check if it's there
  - Other substances – polysubstance use is the norm
    - Cocaine (COC), Amphetamines (AMP), Methamphetamines (MET)
    - Benzodiazepines (BZO)
    - Marijuana (THC)
    - Other sedatives
      - Alcohol, gabapentin, OTCs (diphenhydramine)
      - Sedative effect, important to identify
      - not identified on immunoassay. will show up on comprehensive GC/MS

Using, **interpreting** and responding to urine drug screens

- What the results mean:
  - Benzodiazepines and cannabinoids may persist in urine for several weeks
  - All other substances typically clear within 1-4 days
  - Clonazepam is NOT reliably detected on benzodiazepine immunoassay (POC or lab-based)
    - is detected on GC-MS (comprehensive)
  - Diazepam breaks down to tempazepam and oxazepam
  - Fentanyl, carfentanyl, oxycodone and all synthetic opioids are NOT reliably detected on the MOP/opiate immunoassay, require separate tests
  - False positives are possible
    - amphetamines/methamphetamines
      - Ranitidine, pseudoephedrine, bupropion, venlafaxine
    - MOP/opiates
      - Poppy seeds, quinolones
  - False negatives also occur
    - If results from POC or immunoassay are unexpected, send for GC-MS and/or call the lab
  - Buprenorphine is NOT reliably detected currently on GC-MS/comprehensive (in MB)

Using, interpreting and **responding** to urine drug screens

- Discuss UDS results inconsistent with reported use
  - Consider false positives and false negatives
  - Send for comprehensive when discordant results
- Consistent UDS + for opioids may reflect sub-therapeutic dosing
- Relapses are common and part of recovery – discuss openly to help with relapse prevention planning
- If ongoing opioid or other substance use, remove carries (if present)
  - If inability to provide UDS, consider it + for something
- If urine is cold, or creatinine is low
  - ? Tampered sample
- If negative for prescribed buprenorphine/methadone, benzos etc.
  - Confirm by comprehensive, if confirmed negative
    - Remove carries & decrease dose
    - Discontinuing prescribing

Managing concurrent substance use

- Counseling, mutual support groups, residential & community based treatment
  - Be aware of your local resources & referral pathways
- Pharmacotherapy
  - Alcohol
    - Acamprosate for relapse prevention
  - Nicotine
    - Combined nicotine replacement
    - Varenicline
    - Bupropion

Insomnia

- Difficulties with sleep are common
- Goal = manage insomnia without benzos & z-drugs (which don't work anyway!)
- Consider treating concurrent issues:
  - During stabilization phase withdrawal symptoms cause disturbed sleep
    - Clonidine 0.1 mg HS can be helpful, not for ongoing use
  - PTSD related sleep disturbance
    - Prazosin 1-7mg HS titrated as tolerated (off label use), in addition to SSRI
- **Sleep hygiene including regular routine, behavioural interventions, CBTi**
- Alternative pharmacotherapy (all off label, without good evidence!)
  - Quetiapine 25-50mg
  - Trazodone 50-100mg

References

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