Újdonságok az inszomnia gyógyszeres terápiájában

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Kezelési irányelvek, alapelvek:

Alapelv: Oki kezelés!

Keresni a lehetséges organikus hátteret!

Inszomniák kezelésének legfőbb pillérei:

-Alváshigiéne rendezése

- Magatartásterápia

- Gyógyszeres terápia

Organikus inszomnia esetén is gyakran kiegészítő gyógyszeres kezelés

Kezelési irányelvek, alapelvek:

Ha altató is szükséges:

- Lehető legkisebb dózisban
- Legrövidebb ideig (max. 4 hét – jelenlegi ajánlás vs. tapasztalat)
- Intermittáló kezelés (néhány hét után szünet)

Tranziens és rövid távú inszomniák!

Krónikussá váló inszomnia esetén diagnózis és terápia revizió

Korszerű altatók:

- Rövid és közepes felezési idejű benzodiazepin
- Benzodiazepin receptor agonisták (Z szerek)

A gyógyszeres terápiák alkalmazásainak tévútjai:

A páciensek „követik el”, feltehetően a nem megfelelő tájékoztatás miatt

Lehetőségek:

- Az óvatos duhaj…
  „csak egy fél tabláttát veszek be”
  - nincs elégséges gyógyszerszint

- A mazohista…
  „órákig szenvedek, mielőtt beveszem a gyógyszert” -
  - a kondícionálás működik

- A kísérletező…
  „először csak felet veszek be, majd hajnalban, ha nem tudok aludni, a másik felét is”
  - tönkreteszi a másnapját

Altatóhasználati trendek:

1970-90:	DBZ felhasználás csökkent (függőség)
	50%-os csökkenés
	Helyette szedatív antidepresszánsok használata emelkedett (trazodon, off label)
	A hatásosságáról nem volt megfelelő vizsgálat
	150%-os emelkedés
1999-2010:	1. BzDRA (zolpidem) 2. Trazodone 3. BZD 4. Quentiapine

Altató hatásosság: objektív vs. klinikum

A hatásosság megítélése összetett

Nincs egyértelműen megbízható módszer, változó.

- Kérdőíves módszerek
- PSG (SO, TST, WASO)

De: szubjektív és objektív megítélés különbsége

- Nappali éberségi szint és kognitív teljesítmény szerepe
- Nem panaszos rossz alvók

Benzodiazepin típusu altatók:

	Dózis	Féléletidő	Ürülési sebesség	Nappali szedáció
Midazolam	7.5-15 mg	1-3h	gyors	nincs
Cinolazepam	40mg	4-9h	gyors	lehet
Nitrazepam	5-10mg	30h	lassú	jelentős

Z-szerek:

	Dózis	Féléletidő	Ürülési sebesség	Nappali szedáció
Zaleplon	10mg	kb.1h	gyors	nincs
Zolpidem	10-20 mg	1.5-3h	gyors	lehet
Zopiclone	7.5-15mg	3.5-6h	gyors	lehet
Eszopiclone	2-3mg	6h	gyors	lehet

Melatonin receptor agonista:
- -Ramelteon
- -FDA elalvás előseg-tése
- -Cirkadián alvászavarok
- -CR forma hatásosabb
- -Napközbeni szedáció!!

Szelektív H1 Agonisták:
- -Eredetileg antidepresszáns
- -Nappali szedáció

Orexin receptor antagonisták:
- -Orexin hiánya – Narkolepszia
- -Sucvorexant
  - -OR A és B antagonizmus
- -Nappali szedáció

Antidepresszánsok:
- -Mitrazapin, Doxepin, Trazodone
- -Nappali szedáció, vérnyomásesés

Antipszichotikumok:
- -Risperidone, Olanzapine, Quentiapine

Nonszelektív antihizstaminok:
- -diphenhyramin
- -kizárólag terhesség alatt

AASM ajánlás

Recommended for Treating Sleep Onset Insomnia	
Eszopiclone	**Sleep latency:** Mean reduction was 14 min greater, compared to placebo (95% CI: 3 to 24 min reduction); **Quality of sleep*:** Moderate-to-Large[a] improvement in quality of sleep, compared to placebo; **Side effects:** See Recommendation 2, "Harms" *This recommendation is based on trials of 2 mg and 3 mg doses of eszopiclone.*
Ramelteon	**Sleep latency:** Mean reduction was 9 min greater, compared to placebo (95% CI: 6 to 12 min reduction); **Quality of sleep*:** No improvement[b] in quality of sleep, compared to placebo; **Side effects:** See Recommendation 7, "Harms" *This recommendation is based on trials of 8 mg doses of ramelteon.*
Temazepam	**Sleep latency:** Mean reduction was 37 min greater, compared to placebo (95% CI: 21 to 53 min reduction); **Quality of sleep*:** Small[a] improvement in quality of sleep, compared to placebo; **Side effects:** See Recommendation 6, "Harms" *This recommendation is based on trials of 15 mg doses of temazepam.*
Triazolam	**Sleep latency*:** Mean reduction was 9 min greater, compared to placebo (95% CI: 4 to 22 min reduction); **Quality of sleep*:** Moderate[c] improvement in quality of sleep, compared to placebo; **Side effects:** See Recommendation 5, "Harms" *This recommendation is based on trials of 0.25 mg doses of triazolam.*
Zaleplon	**Sleep latency:** Mean reduction was 10 min greater, compared to placebo (95% CI: 0 to 19 min reduction); **Quality of sleep*:** No improvement[b] in quality of sleep, compared to placebo; **Side effects:** See Recommendation 3, "Harms" *This recommendation is based on trials of 5 mg and 10 mg doses of zaleplon.*
Zolpidem	**Sleep latency:** Mean reduction was 5–12 min greater, compared to placebo (95% CI: 0 to 19 min reduction); **Quality of sleep*:** Moderate[a] improvement in quality of sleep, compared to placebo; **Side effects:** See Recommendation 4, "Harms" *This recommendation is based on trials of 10 mg doses of zolpidem.*

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Recommended for Treating Sleep Maintenance Insomnia	
Doxepin	**Total sleep time:** Mean improvement was 26–32 min longer, compared to placebo (95% CI: 18 to 40 min improvement); **Wake after sleep onset:** Mean reduction was 22–23 min greater, compared to placebo (95% CI: 14 to 30 min reduction); **Quality of sleep*:** Small-to-moderate [a] improvement in quality of sleep, compared to placebo; **Side effects:** See Recommendation 8, "Harms" *This recommendation is based on trials of 3 mg and 6 mg doses of doxepin.*
Eszopiclone	**Total sleep time:** Mean improvement was 28–57 min longer, compared to placebo (95% CI: 18 to 76 min improvement); **Wake after sleep onset:** Mean reduction was 10–14 min greater, compared to placebo (95% CI: 2 to 18 min reduction); **Quality of sleep*:** Moderate-to-Large [a] improvement in quality of sleep, compared to placebo; **Side effects:** See Recommendation 2, "Harms" *This recommendation is based on trials of 2 mg and 3 mg doses of eszopiclone.*
Temazepam	**Total sleep time:** Mean improvement was 99 min longer, compared to placebo (95% CI: 63 to 135 min improvement); **Wake after sleep onset:** Not reported; **Quality of sleep*:** Small [a] improvement in quality of sleep, compared to placebo; **Side effects:** See Recommendation 6, "Harms" *This recommendation is based on trials of 15 mg doses of temazepam.*
Suvorexant	**Total sleep time:** Mean improvement was 10 min longer, compared to placebo (95% CI: 2 to 19 min improvement); **Wake after sleep onset:** Mean reduction was 16–28 min greater, compared to placebo (95% CI: 7 to 43 min reduction); **Quality of sleep*:** Not reported; **Side effects:** See Recommendation 1, "Harms" *This recommendation is based on trials of 10, 15/20, and 20 mg doses of suvorexant.*
Zolpidem	**Total sleep time:** Mean improvement was 29 min. longer, compared to placebo (95% CI: 11 to 47 min. improvement); **Wake after sleep onset:** Mean reduction was 25 min greater, compared to placebo (95% CI: 18 to 33 min reduction); **Quality of sleep*:** Moderate [a] improvement in quality of sleep, compared to placebo; **Side effects:** See Recommendation 4, "Harms" *This recommendation is based on trials of 10 mg doses of zolpidem.*

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Not Recommended for Treating either Sleep Onset or Sleep Maintenance Insomnia	
Diphenhydramine	**Sleep latency:** Mean reduction was 8 min greater, compared to placebo (95% CI: 2 min increase to 17 min reduction); **Total sleep time:** Mean improvement was 12 min longer, compared to placebo (95% CI: 13 min reduction to 38 min improvement); **Quality of sleep*:** No improvement[a] in quality of sleep, compared to placebo; **Side effects:** See Recommendation 11, "Harms" *This recommendation is based on trials of 50 mg doses of diphenhydramine.*
Melatonin	**Sleep latency:** Mean reduction was 9 min greater, compared to placebo (95% CI: 2 to 15 min reduction); **Quality of sleep*:** Small[a] improvement in quality of sleep, compared to placebo; **Side effects:** See Recommendation 12, "Harms" *This recommendation is based on trials of 2 mg doses of melatonin.*
Tiagabine	**Total sleep time:** Mean improvement was 1–7 min longer, compared to placebo (95% CI: 7 min reduction to 15 min improvement); **Wake after sleep onset:** Mean reduction was 1–9 min greater, compared to placebo (95% CI: 6 min increase to 25 min reduction); **Quality of sleep*:** No-to-Small[a] improvement in quality of sleep, compared to placebo; **Side effects:** See Recommendation 10, "Harms" *This recommendation is based on trials of 4 mg doses of tiagabine.*
Trazodone	**Sleep latency*:** Mean reduction was 10 min greater, compared to placebo (95% CI: 9 to 11 min reduction); **Wake after sleep onset:** Mean reduction was 8 min greater, compared to placebo (95% CI: 7 to 9 min reduction); **Quality of sleep*:** No improvement[d] in quality of sleep, compared to placebo; **Side effects:** See Recommendation 9, "Harms" *This recommendation is based on trials of 50 mg doses of trazodone.*
L-tryptophan	**Sleep latency:** Not reported; **Wake after sleep onset*:** Mean reduction was 10 min greater, compared to placebo (95% CI: 4 to 15 min reduction); **Quality of sleep*:** Small[e] improvement in quality of sleep, compared to placebo; **Side effects:** see Recommendation 13, "Harms" *This recommendation is based on trials of 250 mg doses of tryptophan.*
Valerian	**Sleep latency:** Mean reduction was 9 min greater, compared to placebo (95% CI: 0 to 18 min reduction); **Quality of sleep*:** Not reported; **Side effects:** See Recommendation 14, "Harms" *This recommendation is based on trials of variable dosages of valerian and valerian-hops combination.*

ESRS ajánlás

Table 8 Major drug classes used to treat insomnia in Europe

BZ	Diazepam, flunitrazepam, flurazepam, lormetazepam, nitrazepam, oxazepam, temazepam, triazolam
BZRA	Zaleplone, zolpidem, zopiclone
Antidepressants	Agomelatine, amitriptyline, doxepin, mianserin, mirtazapine, trazodone, trimipramine
Antipsychotics	Chlorprothixene, levomepromazine, melperone, olanzapine, pipamperone, prothipendyl, quetiapine
Antihistamines	Diphenhydramine, doxylamine, hydroxyzine, promethazine
Phytotherapeutics	Hops, melissa, passiflora, valerian
Melatonin receptor agonists	Melatonin, ramelteon, slow-release melatonin

BZ, benzodiazepines; BZRA, benzodiazepine receptor agonists.

Treatment

In the presence of co-morbidities, clinical judgement should decide whether insomnia or the co-morbid condition is treated first, or whether both are treated at the same time.*CBT-I*

CBT-I is recommended as first-line treatment for chronic insomnia in adults of any age (strong recommendation, high-quality evidence).

Pharmacological interventions

A pharmacological intervention can be offered if CBT-I is not effective or not available.

BZ and BZRA

- BZ and BZRA are effective in the short-term treatment of insomnia (≤4 weeks; high-quality evidence).
- The newer BZRA are equally effective as BZ (moderate-quality evidence).
- BZ/BZRA with shorter half-lives may have less side-effects concerning sedation in the morning (moderate-quality evidence).
- Long-term treatment of insomnia with BZ or BZRA is not generally recommended because of a lack of evidence and possible side-effects/risks (strong recommendation, low-quality evidence). In patients using medication on a daily basis, reduction to intermittent dosing is strongly recommended (strong recommendation, low-quality evidence).

Sedating antidepressants

- Sedating antidepressants are effective in the short-term treatment of insomnia; contraindications have to be carefully considered (moderate-quality evidence). Long-term treatment of insomnia with sedating antidepressants is not generally recommended because of a lack of evidence and possible side-effects/risks (strong recommendation, low-quality evidence).

Antihistaminics

- Because of insufficient evidence, antihistaminics are not recommended for insomnia treatment (strong recommendation, low-quality evidence).

Antipsychotics

- Because of insufficient evidence and in light of their side-effects, antipsychotics are not recommended for insomnia treatment (strong recommendation, very low-quality evidence).

Melatonin

- Melatonin is not generally recommended for the treatment of insomnia because of low efficacy (weak recommendation, low-quality evidence).

Phytotherapy

- Valerian and other phytotherapeutics are not recommended for the treatment of insomnia because of poor evidence (weak recommendation, low-quality evidence).

Light therapy and exercise

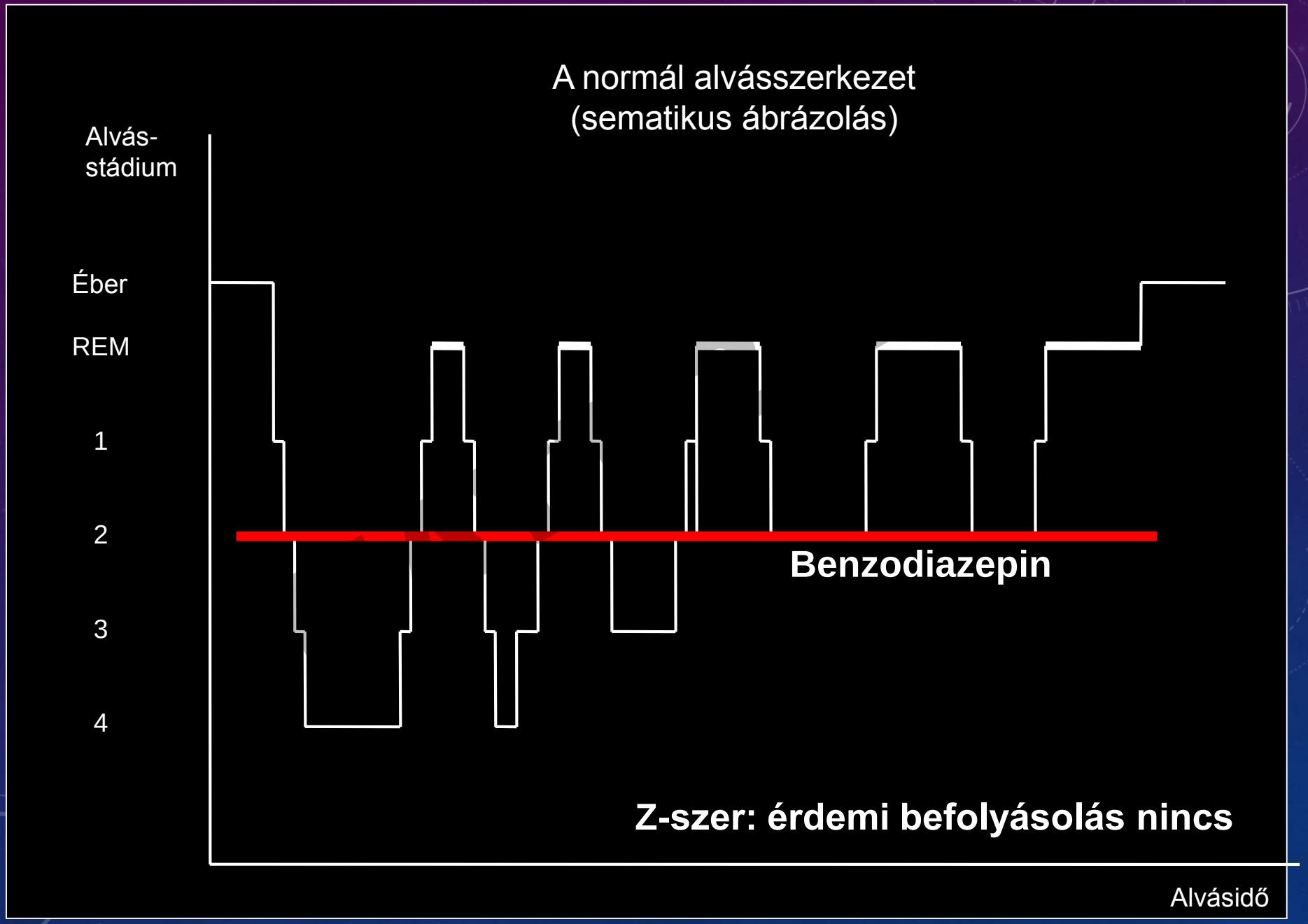
- Light therapy and exercise regimes may be useful as adjunct therapies (weak recommendation, low-quality evidence).

Complementary and alternative medicine

- Acupuncture, aromatherapy, foot reflexology, homeopathy, meditative movement, moxibustion and yoga are not recommended for the treatment of insomnia because of poor evidence (weak recommendation, very low-quality evidence).

BZ, benzodiazepine; BZRA, benzodiazepine receptor agonist; CBT-I, cognitive behavioural therapy for insomnia; CT, Computed Tomography; ECG, electrocardiogram; EEG, electroencephalogram; MRT, Magnetic Resonance Tomography.

Alvásszerkezetre való hatások



Különbégek az elérhető gyógyszerekben: Európa vs. Amerika

2017-es állapot:

Európában nem érhető el: **Orexin receptor antagonista**

DORA

Eszopiclone

2021:

Hazánkban az Eszopiclon elérhető

Krónikus inszomnia – múló panasz?
Avagy, a hosszútávú kezelés jelentősége.

Az organikus háttér nélküli inszomnia gyakran hónapokig, évekig, évtizedekig tartó korlátozottság.

Tapasztalat: A páciensek egy része hosszú évekig szed különféle gyógyszereket, esetleg váltogatva azokat

Jelenlegi irányelvek: Gyógyszer 4 hétig!

A megbízható hosszútávú kezelés fontossága!

Eszopiclone, FDA engedély

2020-óta hazánkban is elérhető

Table 14 Placebo-controlled studies on the long-term intake (at least 12 weeks) of hypnotics

Author (year)	*Sample*	*Substance*	*Duration of treatment*	*Tolerance*	*Abuse dependency*	*Rebound*	*Other undesired side-effects*
Krystal *et al.* (2003)	*N* = 593 (ESZ) *N* = 195 (PLA)	3 mg eszopiclone (39.5% dropouts) Placebo (43.3% dropouts)	6 months	–	–	no (no detailed analysis)	moderate
Perlis *et al.* (2004)	*N* = 98 (ZOLP) *N* = 101 (PLA)	10 mg zolpidem (18.4% dropouts) Placebo (20.7% dropouts)	12 weeks	–	–	no	moderate
Roth *et al.* (2005)	*N* = 471 (ESZ)	Open label ext. ESZ: 17.8% dropouts PLA: 22.5% dropouts	6 + 6 months	–	–	not indicated	moderate
Walsh *et al.* (2007)	*N* = 548 (ESZ) *N* = 280 (PLA)	3 mg eszopiclone (37% dropouts) Placebo (52% dropouts)	6 months	–	–	no – questionable	moderate
Krystal *et al.* (2008)	*N* = 669 (ZOLP) *N* = 349 (PLA)	12.5 mg zolpidem SR (35.3% dropouts) Placebo (47.6% dropouts)	24 weeks	–	–	no – questionable	moderate
Mayer *et al.* (2009)	*N* = 227 (RAM) *N* = 224 (PLA)	8 mg ramelteon (30% dropouts) Placebo (21.4% dropouts)	6 months	–	–	no – questionable	moderate
Ancoli-Israel *et al.* (2010)	*N* = 194 (ESZ) *N* = 194 (PLA)	2 mg eszopiclone (24.2% dropouts) Placebo (elderly) (23.7% dropouts)	12 weeks	–	–	no – questionable	moderate
Krystal *et al.* (2010)	*N* = 159 (DOX) *N* = 81 (PLA)	1/3 mg doxepin (10% dropouts) Placebo (14% dropouts)	12 weeks	–	–	no	moderate
Roehrs *et al.* (2011)	*N* = 17 (ZOLP) *N* = 16 (PLA)	5/10 mg zolpidem (17.6% dropouts) Placebo (12.5% dropouts)	12 months	–	no dose escalation	no indication	no indication
Randall *et al.* (2012)	*N* = 60 (ZOLP) *N* = 65 (PLA)	10 mg zolpidem (26.7% dropouts) Placebo (27.6% dropouts)	8 months	–	–	no indication	no indication
Uchimura *et al.* (2012)	*N* = 164 (ESZ) *N* = 161 (ESZ)	1/2/3 mg eszopiclone (about 15% dropouts)	24 weeks	–	–	no – questionable	moderate
Michelson *et al.* (2014)	*N* = 522 (SUV) *N* = 259 (PLA)	30/40 mg suvorexant (38% dropouts) Placebo (37% dropouts)	12 months	–	–	no – but stronger under suvorexant	moderate – cave: hypersomnia

További fejlesztések:

Zolpidem	-módosítot felszabadulási forma (tablet in tablet)
	-alacsony dózisú forma (midnight insomnia)
	-intranazális oldat
	-buccális aerosol spray (gyorsabb felszívódás)
Melatonin + gyógynövény	-fogkrém -több, egyéb kombináció is
Botolinum toxin	-hangulatzavarok (+ alvászavar)

Összefoglalás

Az altatószer használat elterjedt

Gyakori a nem megfelelő alkalmazás

BDZ, Z-szer

Hosszútávú használat gyakorlata

és jelenleg lehetősége is!