[RWD88]

Risk of Zolpidem Use in Adolescents: National cohort study in Korea (2018-2023)

Acute Neuropsychiatric Adverse Events after Zolpidem Prescription

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BACKGROUND AND OBJECTIVES

- Although zolpidem is contradicted in adolescents under 18 years of age, prescriptions are still frequently issued in real-world clinical practice, raising concerns about inappropriate use and potential adverse outcomes.
- Evidence from nationwide real-world data evaluating the neuropsychiatric safety of zolpidem in this age group is currently lacking.
- This study aimed to assess the short-term risk of acute neuropsychiatric adverse events(anxiety/panic, psychotic/hallucination, sleep-related disorder, headache/dizziness) following zolpidem use in adolescents using the Korean NHIS nationwide database.

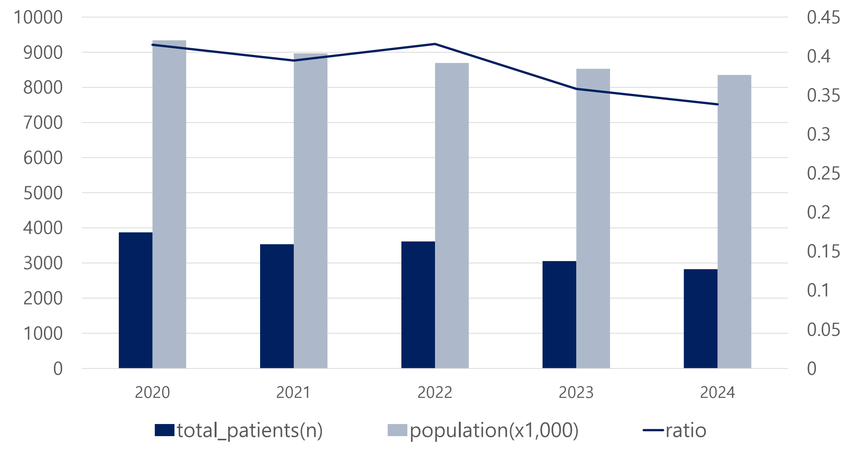

Figure 1. Trends of Zolpidem exposure in pediatric insomnia patients

METHOD

- Design: Retrospective cohort study, NHIS DB (2018-2023)
- Population:
  - Insomnia patients <18 years (ICD-10: F51.0, G47.0)
  - Excluded if each study outcome event occurred within 1 year before index date
- Washout: First 6 months (Jan 1-Jun 30, 2018)
- Exposed group: First zolpidem prescription during study period
- Control group: Insomnia patients without zolpidem or other hypnotics
- Matching: 1:2 PS matching (sex, age, insurance type, psychiatric comorbidities)
- Follow-up period: From index date until the earliest of (1) event occurrence, (2) death, (3) 90 days after index date, or (4) study end date(Dec 31, 2023)
- Analysis:
  - Time-varying Cox Proportional Hazard model
  - Risk Windows: Acute(0-2d), Early(3-14d), Short(15-28d), Ongoing(29-90d)
  - Subgroup: Age groups (0-5 years, 6-11 years, 12-14 years, 15-17 years)

RESULT

- After propensity score matching, a total of 474 exposed and 945 control patients were included for anxiety/panic; 733 vs 1457 for psychotic/hallucination; 723 vs 1435 for sleep-related disorder; and 440 vs 875 for headache/dizziness.

Table 1. Risk Ratios of Neuropsychiatric Events after Zolpidem Use

Neuropsychiatric Events	Risk Ratio	z-value	p-value
Anxiety/Panic	1.864 (1.419-2.447)	4.478	<.001
Psychotic/Hallucination	2.530 (1.154-5.545)	2.318	0.020
Sleep-related Disorder	3.225 (1.741-5.974)	3.724	<.001
Headache/Dizziness	1.441 (1.020-2.036)	2.073	0.038

- The highest relative risk was observed for sleep-related disorders, followed by psychotic/hallucination.
- All four event categories demonstrated a statistically significant increase compared with controls.

Table 2. Hazard Ratios of Neuropsychiatric Events by Risk Window

Neuropsychiatric Events	Window*	Hazard Ratio	Events, Exposed (n)	Events, Control (n)
Anxiety/Panic	Acute	1.691 (0.564~5.07)	6	7
	Early	**2.85 (1.648~4.927)**	32	23
	Short	**2.015 (1.078~3.766)**	21	22
	Ongoing	1.462 (0.881~2.424)	27	40
Psychotic/ Hallucination	Acute	0.988 (0.089~10.996)	1	2
	Early	2.643 (0.593~11.78)	4	3
	Short	3.32 (0.793~13.892)	5	3
	Ongoing	2.695 (0.599~12.126)	4	3
Sleep-related Disorder	Acute	3.915 (0.353~43.409)	2	1
	Early	**7.236 (2.009~26.063)**	11	3
	Short	2.794 (0.881~8.862)	7	5
	Ongoing	1.728 (0.573~5.21)	6	7
Headache/ Dizziness	Acute	0.786 (0.151~4.089)	2	5
	Early	2.138 (0.994~4.6)	14	13
	Short	1.006 (0.42~2.408)	7	14
	Ongoing	1.4 (0.83~2.36)	27	37

*Window: Acute(day0-2), Early(day3-14), Short(day15-28), Ongoing(day29-90)

- Anxiety/Panic risk was elevated during the early (day 3-14) and short (day 15-28) windows.
- Sleep-related disorder showed the strongest association during the early window.
- Psychotic/hallucination and headache/dizziness demonstrated non-significant trends with wide CIs.

Table 3. Hazard Ratios of Neuropsychiatric Events by Age Group

Neuropsychiatric Events	Age group*	Hazard Ratio	Events, Exposed (n)	Events, Control (n)
Anxiety/Panic	Preschool	NMI*	0	0
	Child	0	0	1
	Middle	2.119 (0.908~4.944)	12	14
	High	**1.97 (1.198~3.237)**	73	76
Psychotic/ Hallucination	Preschool	NMI	0	0
	Child	NMI	0	0
	Middle	1.633 (0.266~10.028)	2	3
	High	**2.877 (1.073~7.717)**	12	8
Sleep-related Disorder	Preschool	NMI	0	0
	Child	NMI	1	0
	Middle	NMI	2	0
	High	**2.799 (1.47~5.33)**	23	16
Headache/ Dizziness	Preschool	NMI	0	0
	Child	0	0	1
	Middle	2.49 (0.493~12.571)	3	3
	High	**1.39 (1.141~1.693)**	45	65

*Age group(years): Preschool(0~5), Child(6~11), Middle(12~14), High(15~17), *NMI: No meaningful incidence

- Older adolescents (15-17 years) showed significantly increased risks across all investigated neuropsychiatric events.
- Results for younger age groups (0-14 years) were inconclusive due to small event counts.

DISCUSSION

- Zolpidem use in adolescents was associated with significantly higher risks of acute neuropsychiatric adverse events, most pronounced in the early period (first 2 weeks) for anxiety/panic and sleep-related disorders.
- Older adolescents (15-17 years) showed the greatest vulnerability.
- Limitations include potential residual confounding, low event counts in younger children, and reliance on claims-based diagnosis codes.

CONCLUSION

Adolescents prescribed zolpidem exhibited higher risks of acute neuropsychiatric adverse events, with the strongest associations observed in the early post-prescription period and among older adolescents. These results emphasized the need for **stricter prescribing oversight and monitoring in pediatric populations**.