우울증 환자에게 benzodiazepine 처방

서울특별시 보라매병원
신지윤

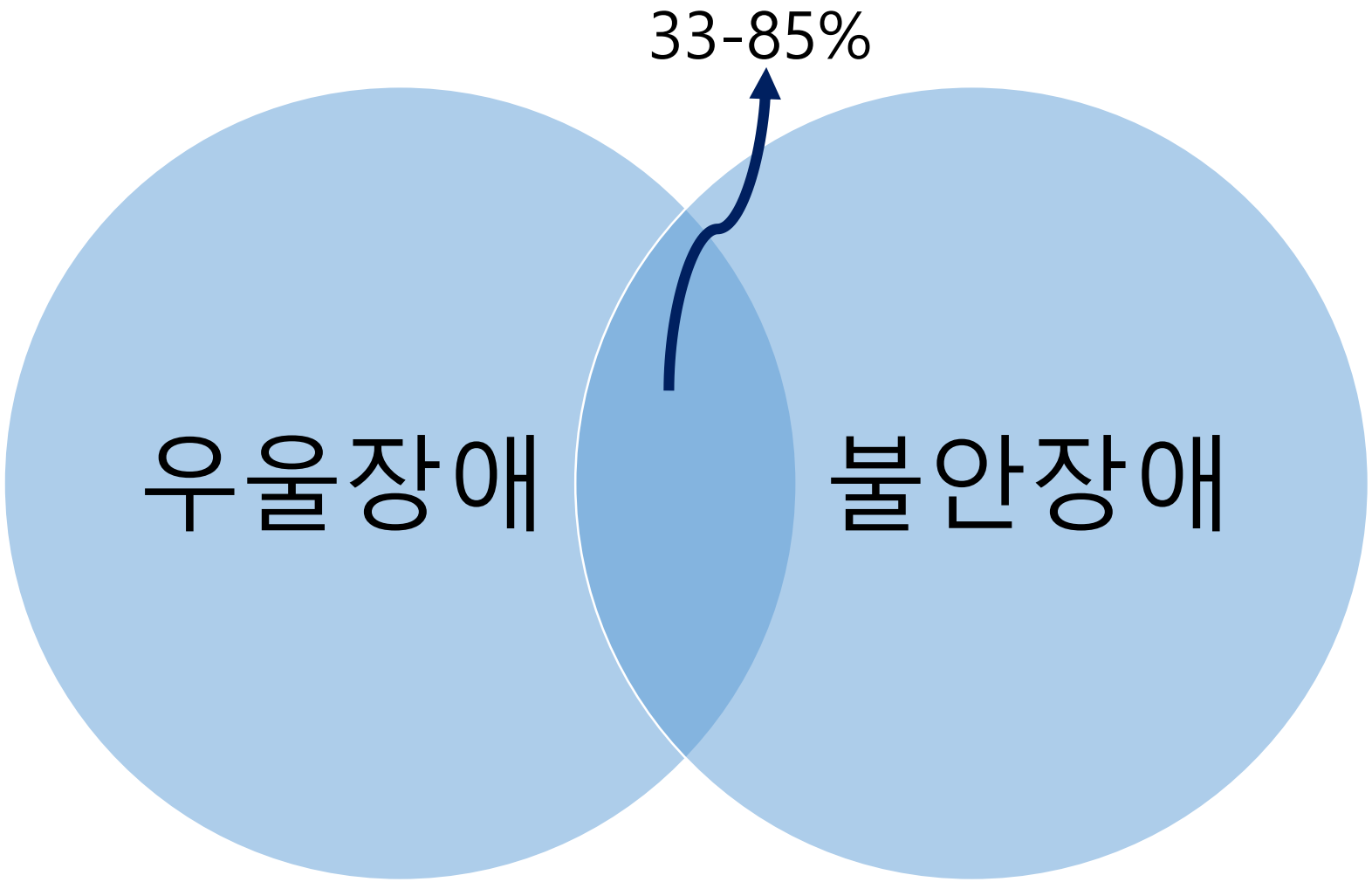
개요

- 우울증에서 benzodiazepine를 사용하는 경우
- 우울증 치료 가이드라인에서의 BDZ 처방
- Cochrane systemic review
- Benzodiazepine의 사용과 tapering

우울증에서 benzodiazepine (BDZ)를 사용하는 경우

- Agitation
  - **Suicidality ↑**
- Generalized anxiety disorder
- Panic disorder
- Insomnia

우울증과 불안장애의 공존



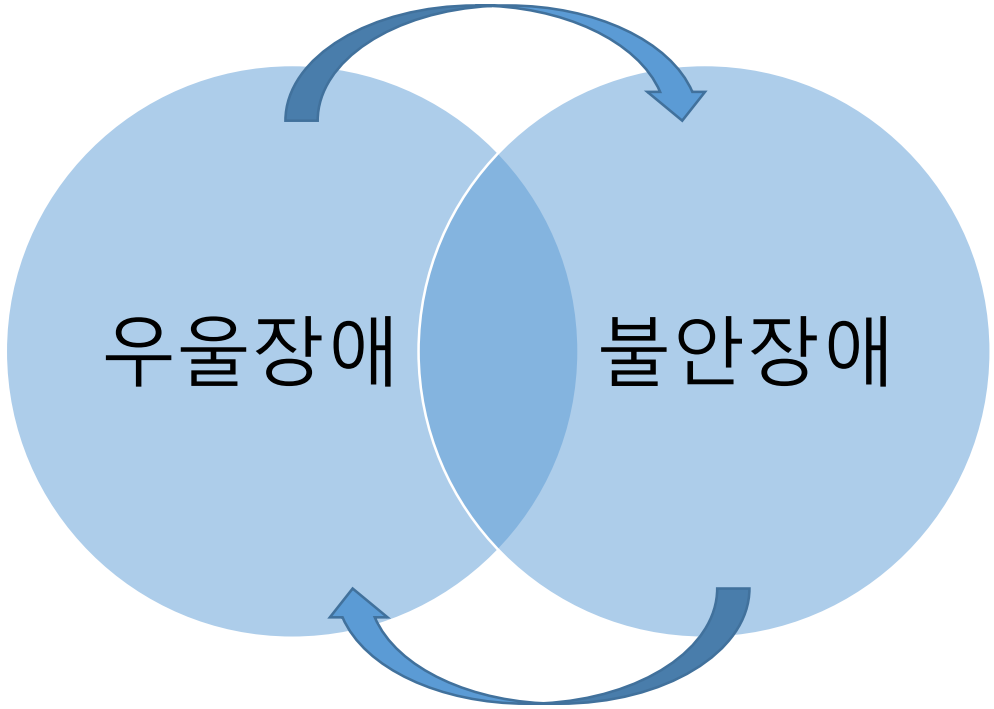
- 증상 심각도↑
- 기능 수준↓
- 치료 반응성↓
- 질병이환 기간↑
- 재발율↑
- 자살위험성↑

)11;72(3):341–348

Comorbidity Patterns of Anxiety and Depressive Disorders in a Large Cohort Study: the Netherlands Study of Depression and Anxiety (NESDA)

Femke Lamers, PhD; Patricia van Oppen, PhD; Hannie C. Comijs, PhD; Johannes H. Smit, PhD; Philip Spinhoven, PhD; Anton J. L. M. van Balkom, MD, PhD; Willem A. Nolen, MD, PhD; Frans G. Zitman, MD, PhD; Aartjan T. F. Beekman, MD, PhD; and Brenda W. J. H. Penninx, PhD

Current anxiety d/o: 67%
A lifetime comorbid anxiety d/o: 75%



Current depressive d/o: 63%
A lifetime comorbid depressive d/o: 81%

- Large cohort, N=1,783
- 공존과 관련 인자
  - Childhood trauma
  - Higher neuroticism
  - Earlier onset of 1st disorder
  - Longer duration of depressive and/or anxiety symptoms
  - Higher symptom severity

J Clin Psychiatry 2011;72(3):341–348

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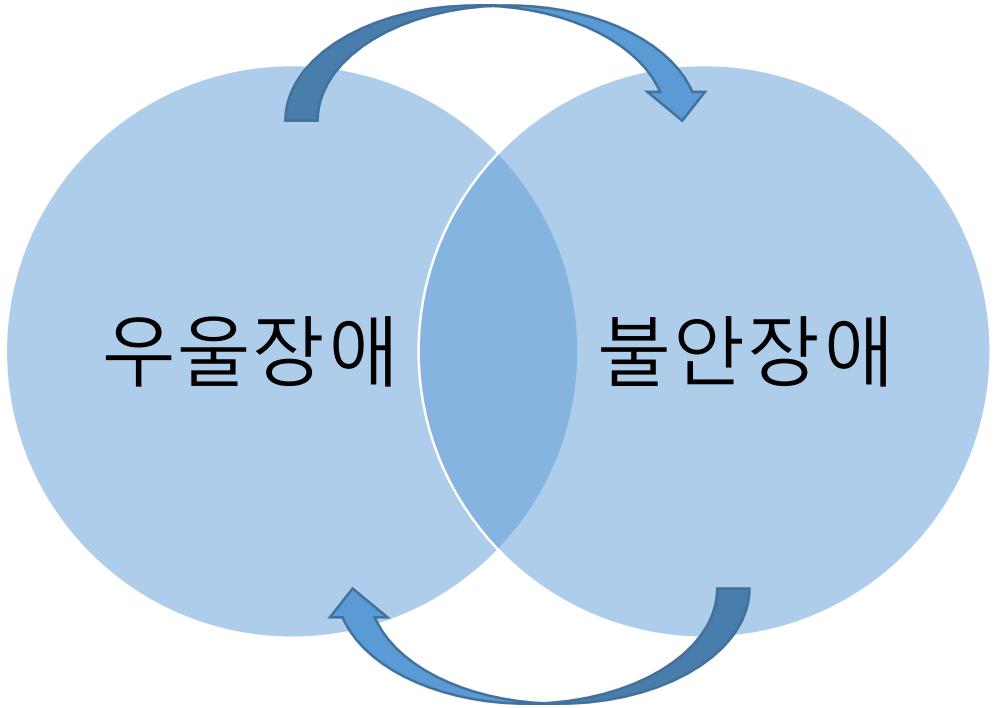

Current depressive d/o: 63%
A lifetime comorbid depressive d/o: 81%

- 57%에서는 불안이 선행
- 18%에서는 우울이 선행

우울증 치료 가이드라인에서의 BDZ 처방

- 현 가이드라인에서는 antidepressant (AD) 단독치료가 1st line pharmacological treatment 에 해당함 (APA 2010; BAP 2015; Baure 2002; NICE 2009)
- 일부 가이드라인에서는 BDZ + AD를 **불안 또는 불면**이 동반된 경우 사용할 수 있는 **제한된 가이드**를 제시함 (APA 2010; BAP 2015, NICE 2009)
  - 동시에 BDZ는 항우울 효과가 없는 것도 함께 명시함 (APA 2010; NICE 2009)
  - BDZ 사용에 따른 다양한 부작용 때문

BDZ의 side effect

- Tolerance, and dependence
- Nocturnal confusion & falls
- Negative effects on cognitive functioning (memory impairment)
- Hangover effects, impairments in driving capability
- Rebound insomnia after withdrawal

임상현장에서의 BZD 처방

- 60%의 정신과 우울증 환자에서 첫 클리닉 방문시 BDZ를 처방 받음 (Furukawa 2000, Japan)
- 지난 12개월간 우울 삽화를 경험한 49.3%에서 AD+BDZ를 사용함 (Sanyal 2011, Canada)

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Cochrane Database of Systematic Reviews 2019, Issue 6. Art. No.: CD001026.
DOI: 10.1002/14651858.CD001026.pub2.

Cochrane Database of Systematic Reviews

[Intervention Review]

Antidepressants plus benzodiazepines for adults with major depression

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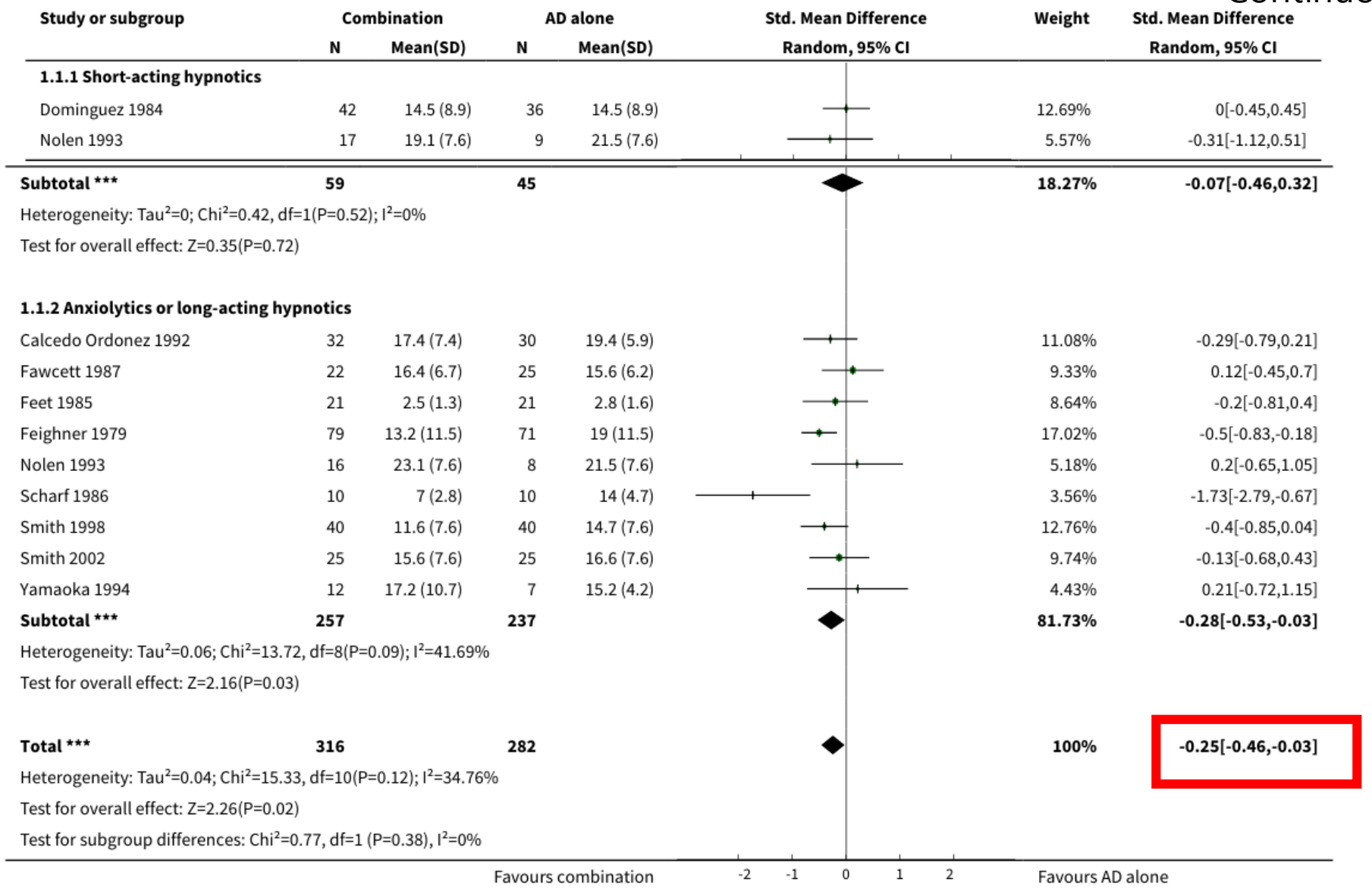
- 2019년도 Cochrane systemic review
- 10 Randomised controlled trials (n = 731)
  - Major depression adults
  - **Combined AD + BDZ** *vs.* **AD alone**

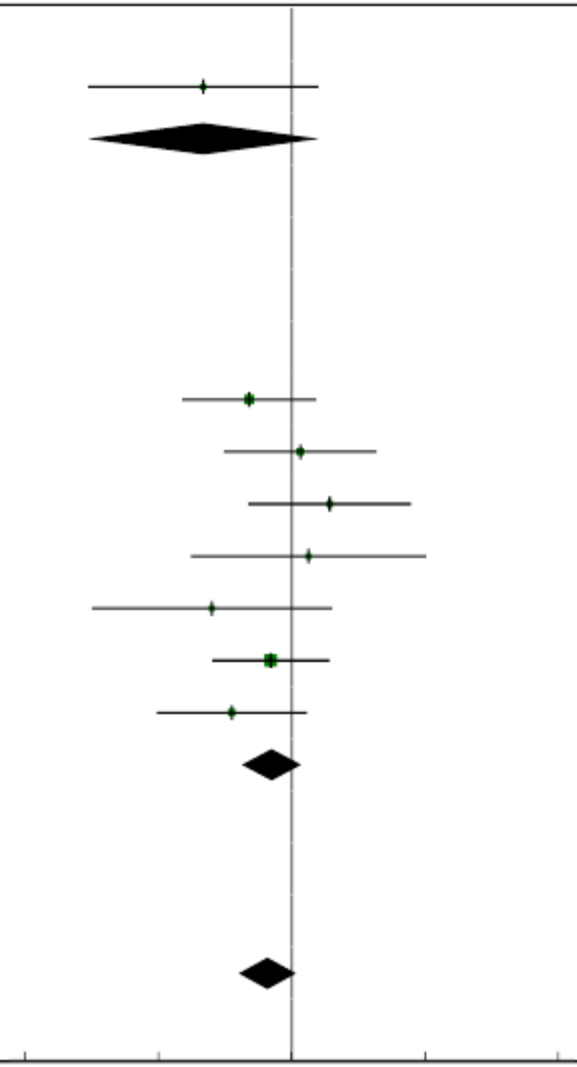
- Early phase: 2 weeks
- Acute phase: 8 weeks
- Continuous phase: >12 weeks

Analysis 1.1. Comparison 1 Combination versus antidepressant (AD) alone: depressive severity, Outcome 1 Early phase (2 weeks, range 1–4 weeks).



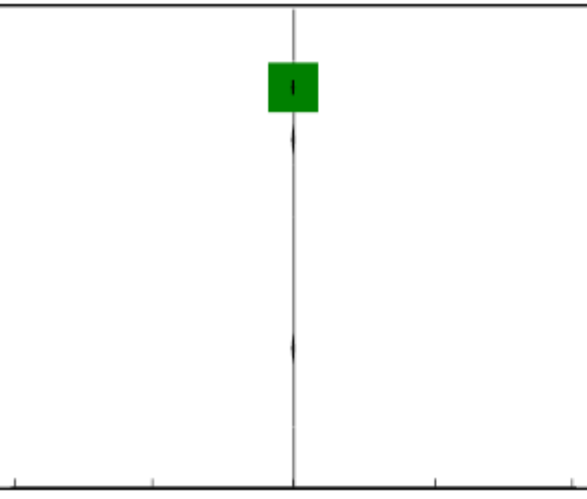
Analysis 1.2. Comparison 1 Combination versus antidepressant (AD) alone: depressive severity, Outcome 2 Acute phase (8 weeks, range 5–12 weeks).

Study or subgroup	Combination N	Combination Mean(SD)	AD alone N	AD alone Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
1.2.1 Short-acting hypnotics							
Nolen 1993	17	16.4 (7.6)	8	21.6 (7.6)		6.11%	-0.66[-1.53,0.2]
Subtotal ***	**17**		**8**			**6.11%**	**-0.66[-1.53,0.2]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.5(P=0.13)							
1.2.2 Anxiolytics or long-acting hypnotics							
Calcedo Ordonez 1992	32	3.7 (3.4)	30	5.3 (6.2)		18.13%	-0.32[-0.82,0.18]
Fawcett 1987	22	13.5 (6.9)	25	13 (8.1)		13.88%	0.06[-0.51,0.64]
Feet 1985	21	1.4 (1.6)	21	1 (1.1)		12.32%	0.29[-0.32,0.89]
Nolen 1993	13	22.6 (7.6)	8	21.6 (7.6)		5.86%	0.13[-0.76,1.01]
Scharf 1986	10	6.7 (2.5)	10	8.6 (3.5)		5.62%	-0.6[-1.5,0.3]
Smith 1998	40	10.1 (7.6)	40	11.3 (7.6)		23.65%	-0.16[-0.6,0.28]
Smith 2002	25	9 (5.2)	25	11.6 (6.1)		14.44%	-0.45[-1.01,0.11]
Subtotal ***	**163**		**159**			**93.89%**	**-0.15[-0.37,0.07]**
Heterogeneity: Tau^2=0; Chi^2=5.36, df=6(P=0.5); I^2=0%							
Test for overall effect: Z=1.34(P=0.18)							
Total ***	**180**		**167**			**100%**	**-0.18[-0.4,0.03]**
Heterogeneity: Tau^2=0; Chi^2=6.63, df=7(P=0.47); I^2=0%							



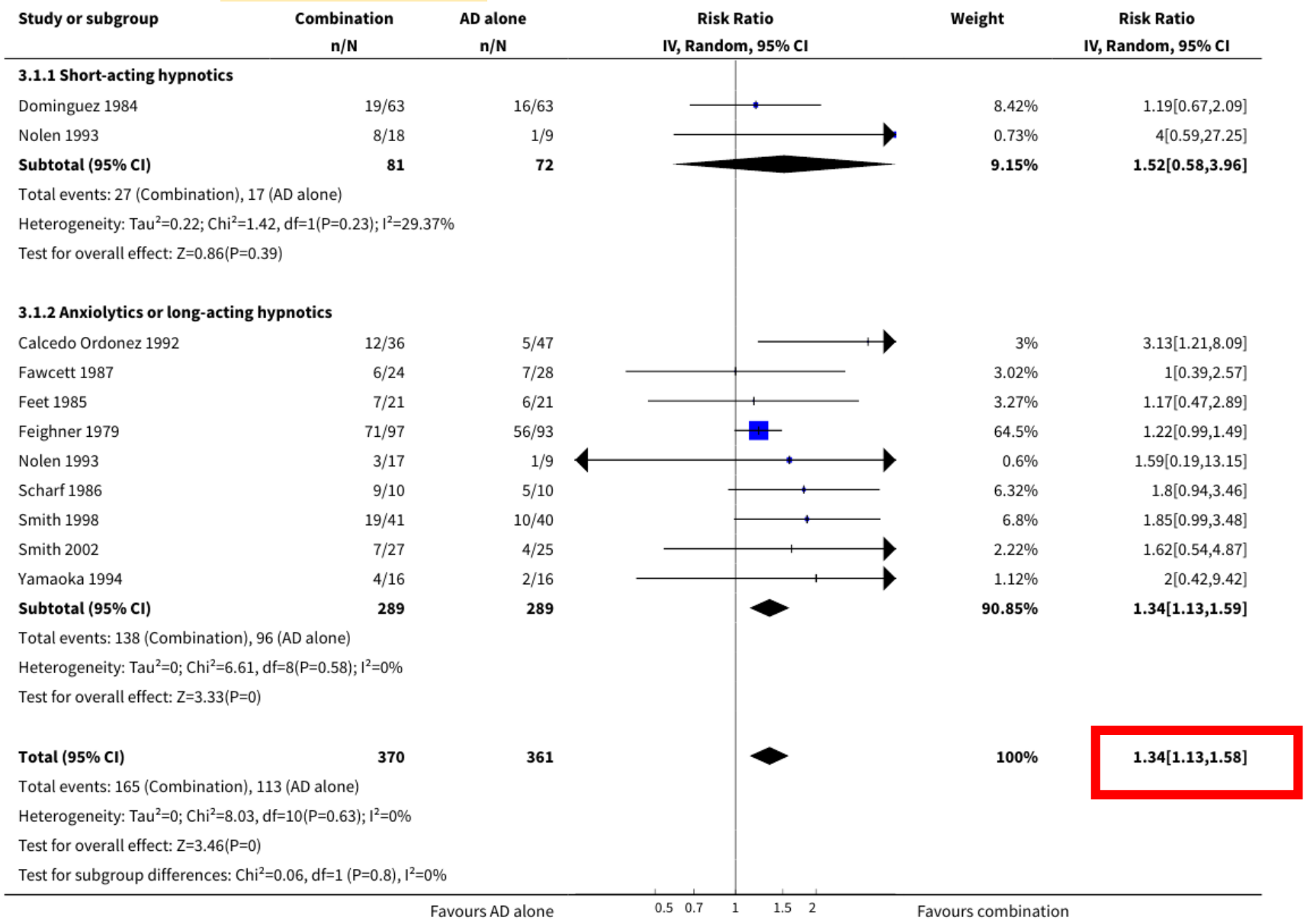
Analysis 1.3. Comparison 1 Combination versus antidepressant (AD) alone: depressive severity, Outcome 3 Continuous phase (> 12 weeks).

Study or subgroup	Combination		AD alone		Std. Mean Difference	Weight	Std. Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI		Random, 95% CI
1.3.1 Anxiolytics or long-acting hypnotics							
Smith 2002	25	8.5 (7.6)	25	10.1 (7.6)		100%	-0.21[-0.76,0.35]
Subtotal ***	**25**		**25**			**100%**	**-0.21[-0.76,0.35]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.73(P=0.46)							
Total ***	**25**		**25**			**100%**	**-0.21[-0.76,0.35]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.73(P=0.46)							

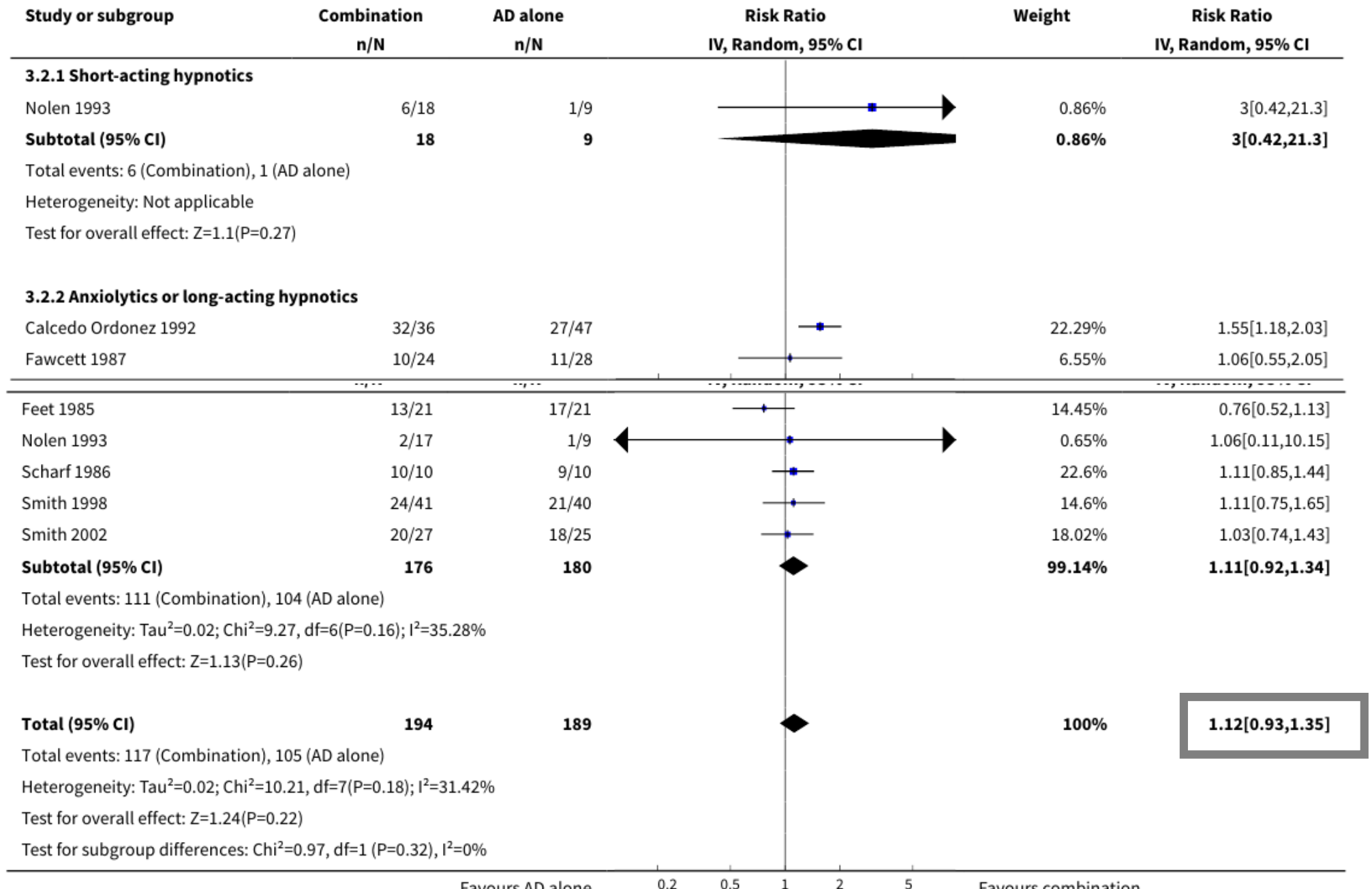


50% reduction in depression severity measures or CGI

Analysis 3.1. Comparison 3 Combination versus antidepressant (AD) alone: response in depression, Outcome 1 Early phase (2 weeks, range 1–4 weeks).

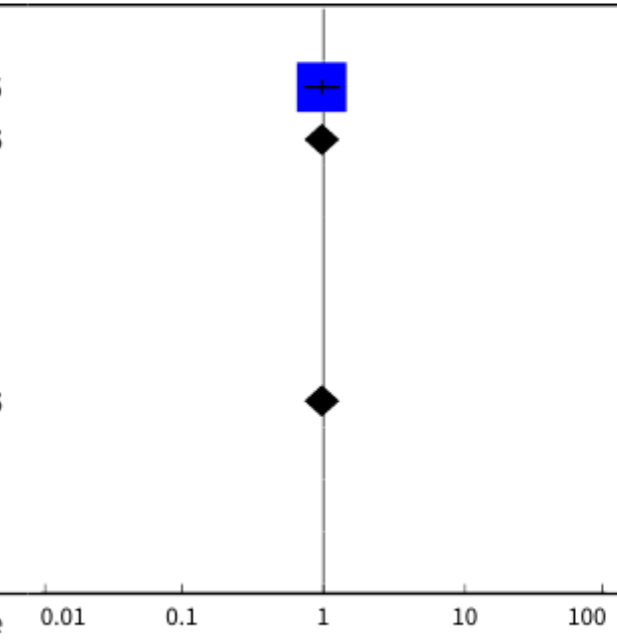


Analysis 3.2. Comparison 3 Combination versus antidepressant (AD) alone: response in depression, Outcome 2 Acute phase (8 weeks, range 5–12 week).



Analysis 3.3. Comparison 3 Combination versus antidepressant (AD) alone: response in depression, Outcome 3 Continuous phase (> 12 weeks).

Study or subgroup	Combination n/N	AD alone n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
3.3.1 Anxiolytics or long-acting hypnotics					
Smith 2002	21/27	20/25		100%	0.97[0.73,1.29]
Subtotal (95% CI)	**27**	**25**		**100%**	**0.97[0.73,1.29]**
Total events: 21 (Combination), 20 (AD alone)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.2(P=0.84)					
Total (95% CI)	**27**	**25**		**100%**	**0.97[0.73,1.29]**
Total events: 21 (Combination), 20 (AD alone)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.2(P=0.84)					



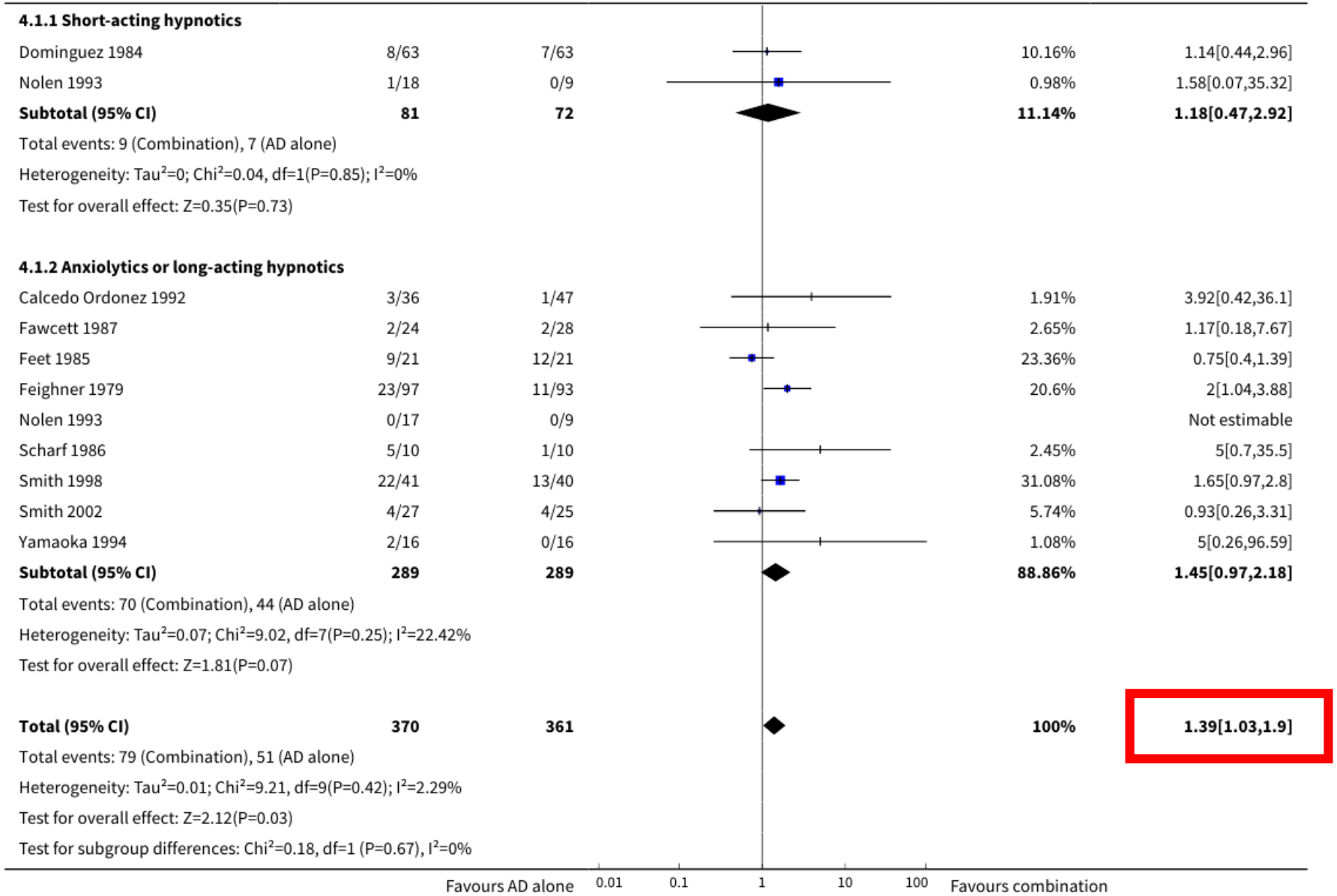
Favours AD alone

Favours combination

7≥ on HRSD or 11≥ MADRS CGI 기준

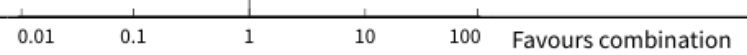
Analysis 4.1. Comparison 4 Combination versus antidepressant (AD) alone: remission in depression, Outcome 1 Early phase (2 weeks, range 1–4 weeks).

Study or subgroup	Combination n/N	AD alone n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
4.1.1 Short-acting hypnotics					
Dominguez 1984	8/63	7/63		10.16%	1.14[0.44,2.96]
Nolen 1993	1/18	0/9		0.98%	1.58[0.07,35.32]
Subtotal (95% CI)	**81**	**72**		**11.14%**	**1.18[0.47,2.92]**
Total events: 9 (Combination), 7 (AD alone)					
Heterogeneity: Tau^2=0; Chi^2=0.04, df=1(P=0.85); I^2=0%					
Test for overall effect: Z=0.35(P=0.73)					
4.1.2 Anxiolytics or long-acting hypnotics					
Calcedo Ordonez 1992	3/36	1/47		1.91%	3.92[0.42,36.1]
Fawcett 1987	2/24	2/28		2.65%	1.17[0.18,7.67]
Feet 1985	9/21	12/21		23.36%	0.75[0.4,1.39]
Feighner 1979	23/97	11/93		20.6%	2[1.04,3.88]
Nolen 1993	0/17	0/9			Not estimable
Scharf 1986	5/10	1/10		2.45%	5[0.7,35.5]
Smith 1998	22/41	13/40		31.08%	1.65[0.97,2.8]
Smith 2002	4/27	4/25		5.74%	0.93[0.26,3.31]
Yamaoka 1994	2/16	0/16		1.08%	5[0.26,96.59]
Subtotal (95% CI)	**289**	**289**		**88.86%**	**1.45[0.97,2.18]**
Total events: 70 (Combination), 44 (AD alone)					
Heterogeneity: Tau^2=0.07; Chi^2=9.02, df=7(P=0.25); I^2=22.42%					
Test for overall effect: Z=1.81(P=0.07)					
Total (95% CI)	**370**	**361**		**100%**	**1.39[1.03,1.9]**
Total events: 79 (Combination), 51 (AD alone)					
Heterogeneity: Tau^2=0.01; Chi^2=9.21, df=9(P=0.42); I^2=2.29%					
Test for overall effect: Z=2.12(P=0.03)					
Test for subgroup differences: Chi^2=0.18, df=1 (P=0.67), I^2=0%					



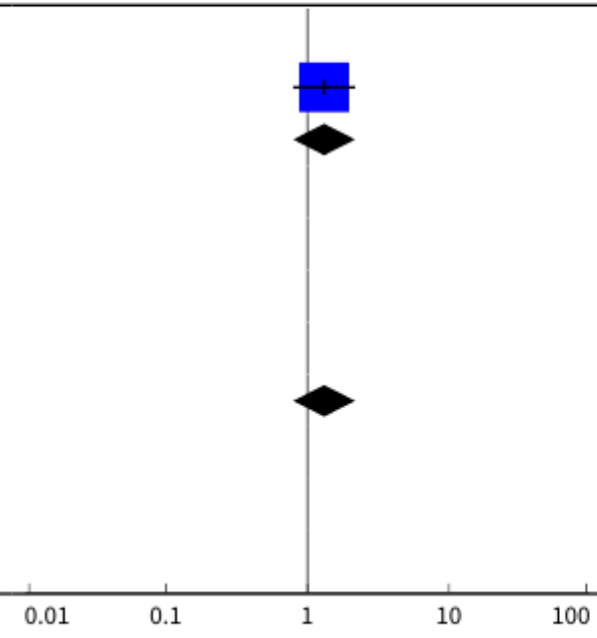
Analysis 4.2. Comparison 4 Combination versus antidepressant (AD) alone: remission in depression, Outcome 2 Acute phase (8 weeks, range 5–12 weeks).

Study or subgroup	Combination n/N	AD alone n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
4.2.1 Short-acting hypnotics					
Nolen 1993	2/18	0/9		0.72%	2.63[0.14,49.69]
Subtotal (95% CI)	**18**	**9**		**0.72%**	**2.63[0.14,49.69]**
Total events: 2 (Combination), 0 (AD alone)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.65(P=0.52)					
4.2.2 Anxiolytics or long-acting hypnotics					
Calcedo Ordonez 1992	27/36	18/47		23.06%	1.96[1.3,2.95]
Fawcett 1987	4/24	6/28		4.46%	0.78[0.25,2.44]
Feet 1985	14/21	14/21		21.8%	1[0.65,1.53]
Nolen 1993	0/17	0/9			Not estimable
Scharf 1986	6/10	3/10		5%	2[0.68,5.85]
Smith 1998	28/41	25/40		30.45%	1.09[0.8,1.5]
Smith 2002	14/27	11/25		14.51%	1.18[0.66,2.09]
Subtotal (95% CI)	**176**	**180**		**99.28%**	**1.26[0.96,1.65]**
Total events: 93 (Combination), 77 (AD alone)					
Heterogeneity: Tau^2=0.04; Chi^2=7.8, df=5(P=0.17); I^2=35.92%					
Test for overall effect: Z=1.69(P=0.09)					
Total (95% CI)	**194**	**189**		**100%**	**1.27[0.99,1.63]**
Total events: 95 (Combination), 77 (AD alone)					
Heterogeneity: Tau^2=0.03; Chi^2=8.05, df=6(P=0.23); I^2=25.45%					
Test for overall effect: Z=1.85(P=0.06)					
Test for subgroup differences: Chi^2=0.24, df=1 (P=0.63), I^2=0%					



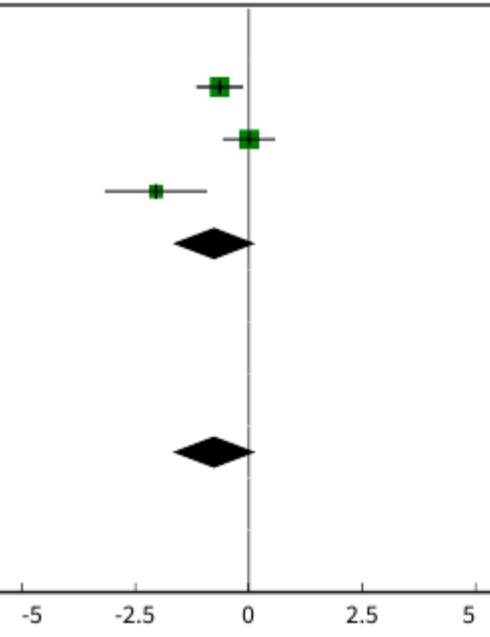
Analysis 4.3. Comparison 4 Combination versus antidepressant (AD) alone: remission in depression, Outcome 3 Continuous phase (> 12 weeks).

Study or subgroup	Combination n/N	AD alone n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
4.3.1 Anxiolytics or long-acting hypnotics					
Smith 2002	17/27	12/25		100%	1.31[0.8,2.16]
Subtotal (95% CI)	**27**	**25**		**100%**	**1.31[0.8,2.16]**
Total events: 17 (Combination), 12 (AD alone)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.06(P=0.29)					
Total (95% CI)	**27**	**25**		**100%**	**1.31[0.8,2.16]**
Total events: 17 (Combination), 12 (AD alone)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.06(P=0.29)					



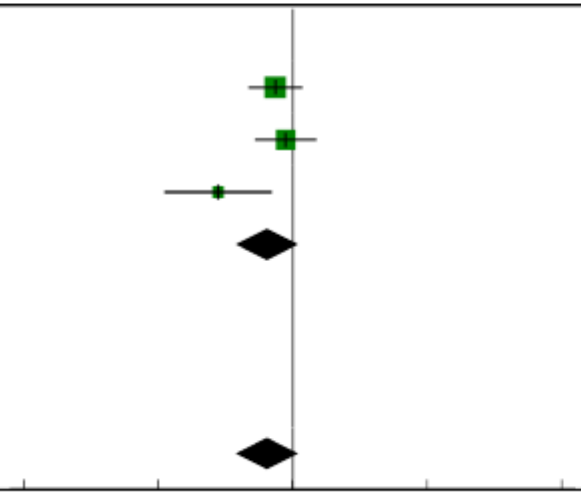
Analysis 5.1. Comparison 5 Combination versus antidepressant (AD) alone: anxiety severity, Outcome 1 Early phase (2 weeks, range 1–4 weeks).

Study or subgroup	Combination N	Combination Mean(SD)	AD alone N	AD alone Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
5.1.1 Anxiolytics or long-acting hypnotics							
Calcedo Ordonez 1992	32	16.4 (7.2)	30	21 (7)		37.67%	-0.64[-1.15,-0.13]
Fawcett 1987	22	17.7 (9.4)	25	17.6 (7.7)		36.55%	0.01[-0.56,0.58]
Scharf 1986	10	36.5 (9.1)	10	55.9 (9.1)		25.77%	-2.04[-3.17,-0.92]
Subtotal ***	**64**		**65**			**100%**	**-0.76[-1.67,0.14]**
Heterogeneity: Tau^2=0.5; Chi^2=10.54, df=2(P=0.01); I^2=81.02%							
Test for overall effect: Z=1.65(P=0.1)							
Total ***	**64**		**65**			**100%**	**-0.76[-1.67,0.14]**
Heterogeneity: Tau^2=0.5; Chi^2=10.54, df=2(P=0.01); I^2=81.02%							
Test for overall effect: Z=1.65(P=0.1)							



Analysis 5.2. Comparison 5 Combination versus antidepressant (AD) alone: anxiety severity, Outcome 2 Acute phase (8 weeks, range 5–12 weeks).

Study or subgroup	Combination		AD alone		Std. Mean Difference	Weight	Std. Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI		Random, 95% CI
5.2.1 Anxiolytics or long-acting hypnotics							
Calcedo Ordonez 1992	32	3.7 (3.4)	30	5.3 (6.1)		41.1%	-0.32[-0.82,0.18]
Fawcett 1987	22	14.8 (8.7)	25	16 (9.1)		37.51%	-0.13[-0.71,0.44]
Scharf 1986	10	35 (14)	10	51.5 (8)		21.39%	-1.39[-2.39,-0.39]
Subtotal ***	**64**		**65**			**100%**	**-0.48[-1.06,0.1]**
Heterogeneity: Tau^2=0.15; Chi^2=4.66, df=2(P=0.1); I^2=57.09%							
Test for overall effect: Z=1.63(P=0.1)							
Total ***	**64**		**65**			**100%**	**-0.48[-1.06,0.1]**



Summary of findings for the main comparison. Antidepressants plus benzodiazepines compared to antidepressants alone for major depression in adults

Antidepressants plus benzodiazepines compared to antidepressants alone for major depression in adults

Patient or population: people with major depression
Setting: inpatients and outpatients
Intervention: antidepressants + benzodiazepines
Comparison: antidepressants alone

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with antidepressants alone	Risk with antidepressants plus benzodiazepines				
Depression severity: early phase (2 weeks, range 1–4 weeks) Follow-up: range 1–4 weeks	—	The mean depression severity in the early phase in the combination group was 0.25 standard deviations lower (0.46 lower to 0.03 lower).	—	598 (10 RCTs)	⊕⊕⊕⊖ **Moderate**[a]	—
Depression severity: acute phase (8 weeks, range 5–12 weeks)	—	The mean depression severity in the acute phase in the combination group was 0.18 standard deviations lower (0.40 lower to 0.03 higher).	—	347 (7 RCTs)	⊕⊕⊖⊖ **Low**[a,b]	—
Depression severity: continuous phase (> 12 weeks)	—	The mean depression severity in the continuous phase in the combination groups was 0.21 standard deviations lower (0.76 lower to 0.35 higher)	—	50 (1 RCT)	⊕⊕⊖⊖ **Low**[a,b]	—
Acceptability of treatment (dropout for any reason)	Study population		**RR 0.76** (0.54 to 1.07)	731 (10 RCTs)	⊕⊕⊕⊖ **Moderate**[a]	—
	332 per 1000	253 per 1000 (180 to 356)				
	Moderate					
	200 per 1000	152 per 1000 (108 to 214)				

Anxiety severity: early phase (2 weeks, range 1–4 weeks)	—	The mean depression severity in early phase in the combination groups was 0.76 standard deviations lower (1.67 lower to 0.14 higher)	—	129 (3 RCTs)	⊕⊝⊝⊝ **Very low**[a,b, c]	—
Adverse effects (dropouts)	Study population		RR 0.54 (0.32 to 0.90)	731 (10 RCTs)	⊕⊕⊕⊝ **Moderate**[a]	—
	119 per 1000	64 per 1000 (38 to 107)				
	Moderate					
	85 per 1000	46 per 1000 (27 to 77)				

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **OR:** odds ratio; **RR:** risk ratio.

GRADE Working Group grades of evidence
High quality: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low quality: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low quality: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]We downgraded the evidence by one level because of risk of bias. Studies were described as "double-blind", but information on the procedure followed to guarantee the blindness, and if blinding was successful, was not reported in all randomised controlled trials. Also, information on randomisation procedures and allocation concealment was lacking in all studies. Moreover, half of the included studies had high attrition rate.
[b]We downgraded the evidence by one level because of low number of participants included in the analysis and 95% confidence interval included both no effect and appreciable benefit.
[c]We downgraded the evidence by one level because of high heterogeneity between studies.

요약

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[Intervention Review]

Antidepressants plus benzodiazepines for adults with major depression

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- **Combined AD + BDZ** *vs.* **AD alone**
  - **Early phase (1-4 weeks) 한정**
  - Depression severity, response in depression, remission in depression 에 더 유효
  - Anxiety severity에 대해서는 차이가 없음
  - Acute phase, prolonged phase 에서는 차이가 없음

BDZ의 half-life

- Anxiety d/o 동반된 경우
  - Long acting BDZ at bedtime
  - Relatively shorter BDZ during daytime
- Sleep-maintenance difficulties
  - Long acting BDZ
- Sleep-onset difficulties
  - Short acting BDZ

Soyka, 2017

Table 1. Pharmacologic Classification and Half-Lives of Representative Benzodiazepines.*

Benzodiazepine	Substance Half-Life	Metabolite Half-Life
	hours	
Hypnotic agents		
Long half-life: flurazepam	2–3	≤100
Intermediate half-life		
Flunitrazepam	10–30	20–30
Nitrazepam	18–30	—
Short half-life		
Brotizolam	3–6	3–6
Lormetazepam	8–14	8–14
Temazepam	7–14	4–15
Very short half-life: triazolam	1.5–5	—
Anxiolytic agents		
Long half-life		
Diazepam	24–48	≤200
Chlordiazepoxide	6–38	≤200
Clobazam	50	20
Clorazepate dipotassium	2–2.5	≤200
Medazepam	2–2.5	≤200
Prazepam	1–3	≤200
Short-to-intermediate half-life with active metabolites		
Lorazepam	2	—
Oxazepam	30	—
Alprazolam	12–15	1
Bromazepam	15	6

* Data on hypnotic agents are from Soyka,[6] Benkert and Hippius,[9] and Julien,[10] and data on anxiolytic agents are from Benkert and Hippius.[9] Dashes denote no active metabolite.

Table 29.9-1
Preparations and Doses of Medications Acting on the Benzodiazepine Receptor Available in the United States

Medication	Brand Name	Dose Equivalent	Usual Adult Dose (mg)	How Supplied
Diazepam	Valium	5	2.5–40.0	2-, 5-, and 10-mg tablets 15-mg slow-release tablets
Clonazepam	Klonopin	0.25	0.5–4.0	0.5-, 1.0-, and 2.0-mg tablets
Alprazolam	Xanax	0.5	0.5–6.0	0.25-, 0.5-, 1.0-, and 2.0-mg tablets 1.5-mg sustained-release tablet
Lorazepam	Ativan	1	0.5–6.0	0.5-, 1.0-, and 2.0-mg tablets 4 mg/mL parenteral
Oxazepam	Serax	15	15–120	7.5-, 10.0-, 15.0-, and 30.0-mg capsules 15-mg tablets
Chlordiazepoxide	Librium	25	10–100	5-, 10-, and 25-mg capsules and tablets
Clorazepate	Tranxene	7.5	15–60	3.75-, 7.50-, and 15.00-mg tablets 11.25- and 22.50-mg slow-release tablets
Midazolam	Versed	0.25	1–50	5 mg/mL parenteral 1-, 2-, 5-, and 10-mL vials
Flurazepam	Dalmane	15	15–30	15- and 30-mg capsules
Temazepam	Restoril	15	7.5–30.0	7.5-, 15.0-, and 30.0-mg capsules
Triazolam	Halcion	0.125	0.125–0.250	0.125- and 0.250-mg tablets
Estazolam	ProSom	1	1–2	1- and 2-mg tablets
Quazepam	Doral	5	7.5–15.0	7.5- and 15.0-mg tablets
Zolpidem	Ambien	10	5–10	5- and 10-mg tablets
	Ambien CR	5	6.25–12.5	6.25- and 12.5-mg tablets
Zaleplon	Sonata	10	5–20	5- and 10-mg capsules
Eszopiclone	Lunesta	1	1–3	1-, 2- and 3-mg tablets
Flumazenil	Romazicon	0.05	0.2–0.5 per min	0.1 mg/mL 5- and 10-mL vials

Kaplan & Sadock's, Synopsis of Psychiatry 10th Edition

BDZ for anxiety

- 1st line pharmacology tx: SSRI
- AD 사용 초반 anxiety, agitation 유발 가능성
- BDZ는 불안을 수분 이내에 호전시킴

Bandelow et al., 2023

Table 7. Dosing recommendations for medication treatment of anxiety disorders, OCD and PTSD.

Treatment	Examples	Recommended daily dose for adults
SSRIs	Citalopram	20–40 mg[a]
	Escitalopram	10–20 mg[a]
	Fluoxetine	20–40 mg
	Fluvoxamine	100–300 mg
	Paroxetine	20–60 mg
	Sertraline	50–200 mg
SNRIs	Venlafaxine	75–225 mg
	Duloxetine	60–120 mg
TCAs	Amitriptyline	75–150 mg
	Clomipramine	75–250 mg
	Imipramine	75–250 mg
	Desipramine	100–300 mg
	Lofepramine	70–210 mg
Benzodiazepines	Alprazolam	1.5–8 mg
	Bromazepam	1.5–6 mg
	Clonazepam	1–4 mg
	Diazepam	5–20 mg
	Lorazepam	2–8 mg
SSRI/5-HT_{1A} receptor partial agonist	Vilazodone	20–40 mg
SARI	Trazodone	150–600 mg
NaSSA	Mirtazapine	30–60 mg
MAOI	Phenelzine	45–90 mg
RIMA	Moclobemide	300–600 mg
MT_1/MT_2 agonist/5-HT_{2C} antagonist	Agomelatine	25–50 mg
Calcium channel modulators	Pregabalin	150–600 mg
	Gabapentin	600–3600 mg
Atypical antipsychotics	Quetiapine	50–300 mg
	Risperidone	0.5–6 mg
	Olanzapine	2.5–20 mg
Antihistamine	Hydroxyzine	37.5–75 mg
Tricyclic anxiolytic	Opipramol	50–150 mg
Azapirone	Buspirone	15–60 mg
Anticonvulsant	Lamotrigine	25–500 mg
Lavender oil extract	Silexan	80–160 mg
α_1-Antagonist	Prazosin	1–10 mg

BDZ for insomnia symptoms

- BDZ & Z-drug는 **4주 이내**의 short-term 사용 권고 (European Insomnia Guideline, 2023)
- 대부분의 meta-analyses 에서 **최대 4주 이내** 사용시 수면에 대한 긍정적 효과가 있었음.

Characteristics of Benzodiazepine Receptor Agonists Commonly Used for Insomnia

Generic Name	Receptor Binding Specificity	Dose Range (mg)	Elimination Half-Life (hr)	Metabolism
Estazolam	Nonspecific	1–2	10–24	CYP3A
Flurazepam	Nonspecific	15–30	48–120 [a]	CYP3A4
Lorazepam [b]	Nonspecific	0.5–2	8–12	CYP3A4
Quazepam	Nonspecific	7.5–15	39–73 [a]	Not available
Temazepam	Nonspecific	15–30	8–20	None
Triazolam	Nonspecific	0.125–0.25	2–6	CYP3A4
Eszopiclone	$GABA_A$, α1,2,3	1–3	6	CYP3A4, CYP2E1
Zaleplon	$GABA_A$, α1	5–20	1	Minor: CYP3A4
Zolpidem	$GABA_A$, α1	5–10	1.5–2.4	CYP3A4, CYP2C9
Zolpidem extended-release	$GABA_A$, α1	6.25–12.5	1.6–4.5	CYP3A4, CYP2C9
Zolpidem sublingual tablet	$GABA_A$, α1	5–10	1.5–2.4	CYP3A4, CYP2C9
Zolpidem oral spray	$GABA_A$, α1	5–10	1.5–2.4	CYP3A4, CYP2C9
Zolpidem sublingual lozenge	$GABA_A$, α1	1.75–3.5	1.5–2.4	CYP3A4, CYP2C9

Principle and practice of Sleep Medicine, 7th edition

Clinical Practice Guideline for the Pharmacologic Treatment of Chronic Insomnia in Adults: An American Academy of Sleep Medicine Clinical Practice Guideline

Michael J. Sateia, MD[1]; Daniel J. Buysse, MD[2]; Andrew D. Krystal, MD, MS[3]; David N. Neubauer, MD[4]; Jonathan L. Heald, MA[5]

Table 5—Summary of "critical" outcomes by indication.

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.*

Tapering BDZ medications

- 4-6주 이상의 기간 동안에 서서히 감량
  - Seizure, severe withdrawal symptoms를 줄이기 위함
- 매주 용량의 50%를 감량하도록 권고
- Short-acting BZD withdrawal 의 경우 long-acting BZD withdrawal 에서보다 drop-out이 높음
- Motivation enhancement 가 필요함

Soyka, 2017

Table 3. Clinical Symptoms and Complications of Benzodiazepine Withdrawal.*

Psychopathologic symptoms
Increased anxiety
Nervousness
Sleep disorders
Inner restlessness
Depressive symptoms
Irritability
Psychosis-like conditions, delirium
Depersonalization and derealization
Confusion
Vegetative symptoms
Trembling
Sweating
Nausea and vomiting
Motor agitation
Dyspnea
Increased heart rate
Elevated blood pressure
Headaches
Muscle tension
Neurologic and physical complications
Increased risk of seizures
Impairment of voluntary movements
Cognitive impairments
Impairment of memory
Pronounced perceptual impairments
Hyperacusis
Photophobia
Hypersomnia
Dysesthesia, kinesthetic disorders, muscle twitching and fasciculations

* Data are from Soyka,[6] Ashton,[45] Lader and Kyriacou,[47] and Soyka and Batra.[49]

요약

- 우울증에는 불안, 불면이 흔하게 동반됨
- BDZ과 AD의 병용은 4주 이내 단기 사용시 우울 심각도, response, remission에서 효과가 있음
- BDZ의 단기적 사용은 불안, 불면에 효과가 있음
- 추후 BDZ를 taper out하는 것에 대한 고민이 필요함

감사합니다