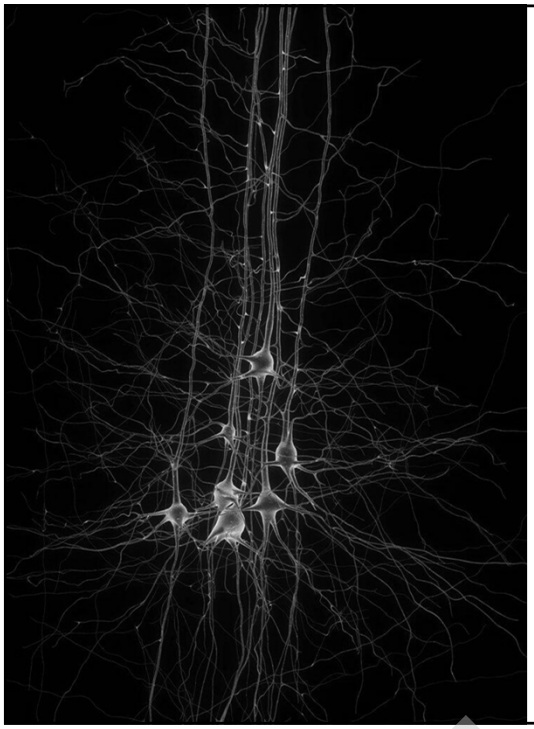

TRASTORNO BIPOLAR TIPO I

EVIDENCIA ACTUAL SOBRE MANEJO DE EPISODIOS AGUDOS, PROFILAXIS Y EVENTOS ADVERSOS

Jorge M Tamayo, M.D., B.Sc.(Pharm.)
Dpto. Psiquiatría, Universidad CES, Medellín, Colombia
Dpto. Psicología, U.P.B., Medellín, Colombia
Dpto. Psicología, Universidad EAFIT. Medellín

Curso e Impacto del Trastorno Bipolar

Curso del Trastorno Bipolar

- Aproximadamente ⅓ se presenta con episodios mixtos[1]
  - Se asocia a menor probabilidad de recuperación y mayor uso de antidepresivos que los estados maníacos puros
- En pacientes (n=53) con un primer episodio de manía:[2]
  - >50% experimentaron recurrencia afectiva durante el primer año de seguimiento (tiempo promedio para el evento: 7.9 meses)
- En 219 pacientes seguidos durante 25 años:[3]
  - Duración promedio de los episodios afectivos en TB-I: 13 sem.

1. Azorin et al. BMC Psychiatry 2009;9:33; 2. Yatham et al. Can J Psychiatry 2009;54:105-12; 3.Solomon et al. Arch Gen Psychiatry 2010;67:339-47

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Correlatos Clínicos de la Polaridad Predominante[1,2]

- Polaridad depresiva
  - 34% de los pacientes
  - Más bipolares II
  - Más debut depresivo
  - Más patrón estacional
  - Más intentos de suicidio
  - Mayor uso de antidepresivos
- Polaridad maníaca
  - 22% de los pacientes
  - Más bipolares I
  - Más debut maníaco
  - Más jóvenes e inicio precoz
  - Más trastornos por uso de sustancias psicoactivas
- La polaridad maníaca se asoció con un número mayor de hospitalizaciones, intentos de suicidio y síntomas psicóticos a lo largo de un período de 7 años vs. pacientes con polaridad depresiva.[3]

1. Colom F et al. J Affect Disord 2006;93:13-17; 2. Rosa AR et al. J Affect Disord 2008;107:45-51; 3. Belizario GO et al. J Affect Disord 2018;241:37–40

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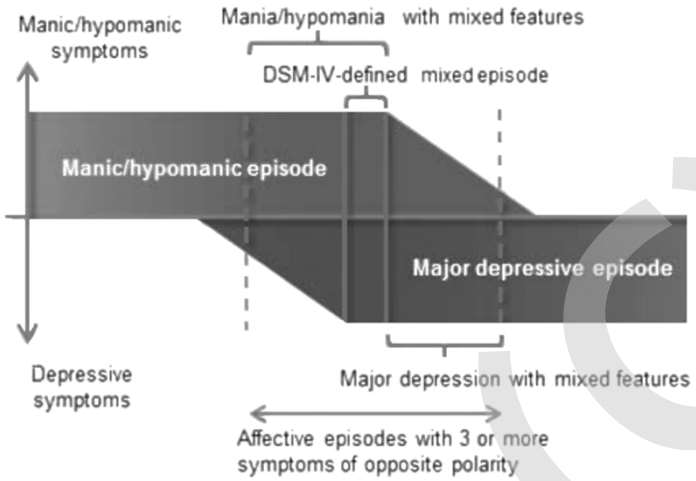
Manía y Depresión Bipolar con Síntomas Mixtos



Takeshima M. CNS Spectr 2017;22:177-185

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Impacto del Trastorno Bipolar

- **Dificultades laborales**
  - **Estudio EMBLEM (European Mania in Bipolar disorder Longitudinal Evaluation of Medication): Discapacidad mayor en el 69% de los pacientes al inicio y en el 41% a los 2 años[1]**
  - **Encuesta global UNITE (Understanding Patients' Needs, Interactions, Treatment, and Expectations): Sólo ⅓ de los pacientes con TB tiene empleo de tiempo completo[2]**
- **Riesgo de Arresto**
  - **Asociado a uso de drogas, pobre cumplimiento de terapia y arrestos previos[3]**
    - **El uso de ASG disminuye el riesgo de arrestos**

1. Reed et al. Eur Psychiatry 2010;25:338-44; 2. McIntyre. J Clin Psychiatry 2009;70:5-11; 3. Van Dorn et al. J Clin Psychiatry 2011;72:502-8

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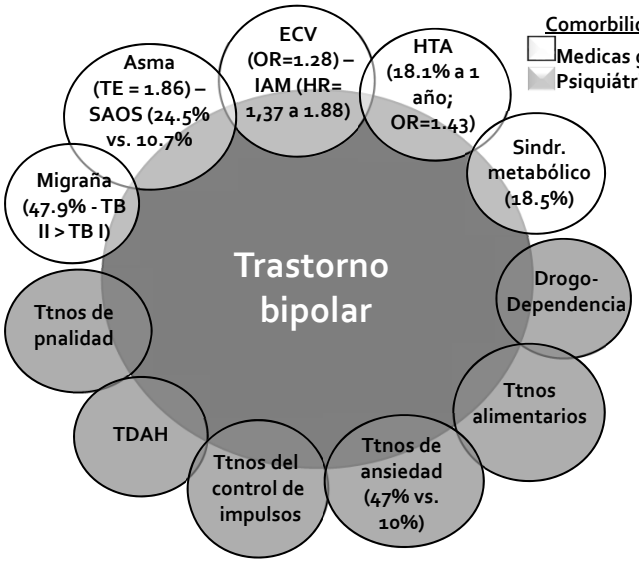
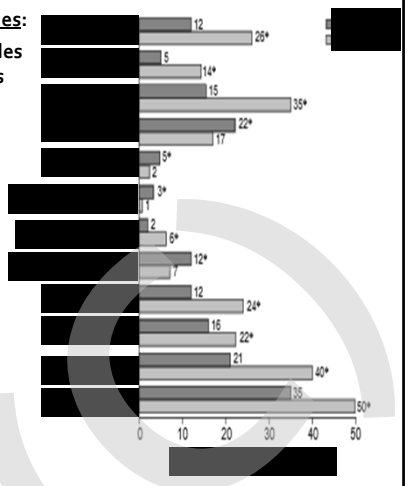
Comorbilidades... La Multidimensionalidad del Trastorno Bipolar





* p>0.05

Krishnan KR. Psychosom Med 2005;67:1-8; Sinha A et al. Curr Psychiatry Rep 2018;20:36; Spoorthy MS et al. World J Psychiatry 2019;9:7-29; Calabrese JR et al. J Clin Psychiatry 2003;64:425-432

Principales Causas de Mortalidad en Pacientes con Trastornos Bipolares (n = 15.386)

Causa	Riesgo Estandarizado de Mortalidad (95% IC)	
	Hombres	Mujeres
Infecciosa	3.4 (1.9-5.8)	2.4 (1.2-4.1)
Respiratoria	3.1 (2.6-3.7)	2.7 (2.1-3.4)
Endocrina	3.2 (2.3-4.4)	2.8 (2.0-3.9)
Cardiovascular	1.9 (1.8-2.1)	2.6 (2.4-2.9)
Cáncer	1.1 (0.9-1.3)	1.2 (1.1-1.4)

Mortalidad vs. controles (Promedio de 16 estudios) = 2.28

Osby U et al. Arch Gen Psychiatry 2001;58:844-850; Goodwin FK, Jamison KR. Manic-Depressive Illness. New York, NY:Oxford University Press; 2007

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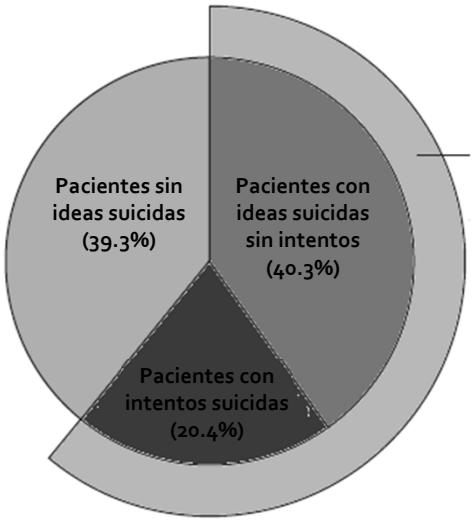
Riesgo de Comportamiento Suicida en Bipolares (Episodio Actual)



Pacientes con ideas suicidas (60.7%)

Jorvi Bipolar Study (JoBS)
bipolar I, N = 90; bipolar II, N = 101

Riesgo a lo largo de la vida:
80% (comportamiento suicida) y 51% (intento suicida)

Valtonen H et al. J Clin Psychiatry 2005;66:1456–1462

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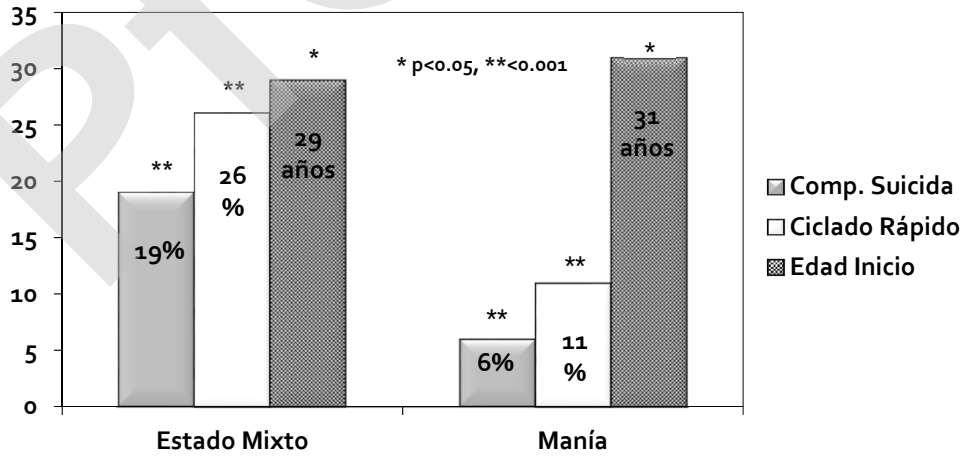
Características de la Manía Mixta (EMBLEM)



Azorin JM. BMC Psychiatry 2009;9:33

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Tratamiento Farmacológico de los Episodios Agudos en Trastorno Bipolar I

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Eutimizantes en Manía Aguda. Meta-Análisis

Drug	Trials	Subjects	Mean Dose (mg/day)	Response (RR [95% CI])	Dropout (RR [95% CI])	
Risperidone	4	976	3.50 ± 0.00	2.66 [1.86–3.81]	0.60 [0.38–0.93]	
Carbamazepine	2	427	700 ± 80.0	2.64 [1.60–4.30]	0.88 [0.51–1.56][a]	X
Haloperidol	9	1663	9.45 ± 5.65	2.47 [1.89–3.25]	0.74 [0.53–1.04][a]	X
Cariprazine	4	1198	7.12 ± 1.89	2.33 [1.56–3.53]	1.04 [0.63–1.73][a]	X
Olanzapine	10	2031	13.4 ± 1.92	2.33 [1.82–3.02]	0.47 [0.35–0.63]	
Aripiprazole	8	1982	22.5 ± 4.74	2.07 [1.56–2.77]	0.68 [0.48–0.96]	
Quetiapine	6	1306	612 ± 118	2.05 [1.49–2.85]	0.63 [0.41–0.94]	
Valproate	7	1299	1431 ± 954	2.05 [1.48–2.87]	0.67 [0.47–0.97]	
Lithium	14	1981	1260 ± 251	1.92 [1.49–2.49]	0.94 [0.69–1.29][a]	X
Paliperidone	5	1157	7.50 ± 3.87	1.72 [1.08–2.74]	0.60 [0.33–1.06][a]	X
Asenapine	4	841	18.3 ± 0.14	1.61 [1.03–2.54]	0.88 [0.51–1.53][a]	X
Ziprasidone	4	839	124 ± 7.21	1.47 [1.06–2.04]	0.93 [0.61–1.41][a]	X

a Abandono por cualquier causa es mayor que con placebo para asenapina, carbamazepina, cariprazina, haloperidol, litio, paliperidona y ziprasidona

Baldessarini RJ et al. Mol Psychiatry 2019;24:198-217

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Eutimizantes en Manía Aguda. Meta-Análisis de Red (n=14256)

Risperidone	0.81 (0.48 to 1.37)	1.28 (0.78 to 2.1)	0.57 (0.29 to 1.14)	0.63 (0.37 to 1.08)	0.67 (0.32 to 1.37)	1 (0.48 to 2.11)	0.88 (0.5 to 1.54)	0.68 (0.34 to 1.36)	0.95 (0.52 to 1.76)	—	0.84 (0.43 to 1.64)	0.89 (0.5 to 1.56)	0.17 (0.02 to 1.1)	0.51 (0.24 to 1.08)	0.47 (0.17 to 1.24)	**0.5 (0.28 to 0.92)**
0.11 (−0.13 to 0.35)	Haloperidol	**1.58 (1.06 to 2.39)**	0.71 (0.39 to 1.31)	0.78 (0.5 to 1.21)	0.83 (0.43 to 1.58)	1.24 (0.64 to 2.45)	1.09 (0.72 to 1.66)	0.84 (0.45 to 1.58)	1.18 (0.71 to 1.98)	—	1.04 (0.59 to 1.82)	1.1 (0.68 to 1.78)	0.21 (0.03 to 1.32)	0.63 (0.32 to 1.26)	0.58 (0.23 to 1.47)	0.74 (0.53 to 1.04)
0.17 (−0.06 to 0.39)	0.06 (−0.14 to 0.25)	Olanzapine	**0.45 (0.25 to 0.81)**	**0.49 (0.33 to 0.73)**	**0.53 (0.28 to 0.97)**	0.78 (0.41 to 1.51)	0.69 (0.44 to 1.07)	**0.53 (0.31 to 0.91)**	0.74 (0.45 to 1.23)	—	0.65 (0.37 to 1.17)	0.69 (0.47 to 1.02)	**0.12 (0.02 to 0.82)**	**0.4 (0.21 to 0.78)**	**0.37 (0.14 to 0.91)**	**0.47 (0.35 to 0.63)**
0.18 (−0.15 to 0.5)	0.07 (−0.24 to 0.36)	0.01 (−0.28 to 0.3)	Cariprazine	1.1 (0.61 to 1.99)	1.17 (0.55 to 2.47)	1.74 (0.81 to 3.81)	1.53 (0.83 to 2.84)	1.18 (0.56 to 2.51)	1.66 (0.87 to 3.23)	—	1.46 (0.71 to 2.99)	1.55 (0.83 to 2.89)	0.3 (0.04 to 1.93)	0.9 (0.41 to 1.97)	0.82 (0.3 to 2.23)	1.04 (0.63 to 1.73)
0.2 (−0.06 to 0.44)	0.09 (−0.13 to 0.29)	0.03 (−0.17 to 0.22)	0.02 (−0.28 to 0.31)	Lithium	1.06 (0.57 to 1.96)	1.58 (0.83 to 3.06)	1.39 (0.9 to 2.17)	1.07 (0.58 to 2.01)	1.51 (0.94 to 2.45)	—	1.33 (0.73 to 2.39)	1.4 (0.89 to 2.2)	0.27 (0.04 to 1.68)	0.81 (0.45 to 1.46)	0.74 (0.29 to 1.86)	0.94 (0.69 to 1.29)
0.21 (−0.13 to 0.56)	0.1 (−0.21 to 0.43)	0.04 (−0.26 to 0.36)	0.03 (−0.33 to 0.42)	0.02 (−0.28 to 0.34)	Carbamazepine	1.48 (0.67 to 3.41)	1.31 (0.68 to 2.54)	1.01 (0.46 to 2.23)	1.41 (0.72 to 2.87)	—	1.24 (0.59 to 2.67)	1.32 (0.7 to 2.53)	0.26 (0.03 to 1.68)	0.76 (0.34 to 1.75)	0.69 (0.25 to 1.97)	0.88 (0.51 to 1.56)
0.28 (−0.08 to 0.63)	0.17 (−0.17 to 0.49)	0.11 (−0.22 to 0.43)	0.1 (−0.28 to 0.49)	0.08 (−0.24 to 0.41)	0.07 (−0.35 to 0.46)	Paliperidone	0.88 (0.44 to 1.72)	0.68 (0.3 to 1.51)	0.95 (0.5 to 1.81)	—	0.84 (0.39 to 1.8)	0.89 (0.44 to 1.75)	0.17 (0.02 to 1.13)	0.51 (0.22 to 1.18)	0.47 (0.16 to 1.32)	0.6 (0.33 to 1.06)
0.27 (0.01 to 0.54)	0.17 (−0.04 to 0.37)	0.11 (−011 to 0.33)	0.1 (−0.21 to 0.41)	0.08 (−0.14 to 0.31)	0.06 (−0.27 to 0.39)	0 (−0.34 to 0.34)	Aripiprazole	0.77 (0.4 to 1.48)	1.08 (0.64 to 1.86)	—	0.95 (0.52 to 1.74)	1.01 (0.61 to 1.66)	0.2 (0.03 to 1.22)	0.58 (0.3 to 1.16)	0.53 (0.21 to 1.35)	**0.68 (0.48 to 0.96)**
0.29 (−0.05 to 0.62)	0.18 (−0.13 to 0.49)	0.12 (−0.15 to 0.39)	0.12 (−0.26 to 0.49)	0.09 (−0.21 to 0.41)	0.08 (−0.32 to 0.46)	0.01 (−0.39 to 0.42)	0.02 (−0.31 to 0.34)	Asenapine	1.4 (0.71 to 2.8)	—	1.23 (0.58 to 2.61)	1.31 (0.69 to 2.46)	0.25 (0.03 to 1.68)	0.76 (0.34 to 1.71)	0.69 (0.25 to 1.92)	0.88 (0.51 to 1.53)
0.3 (0 to 0.58)	0.19 (−0.07 to 0.43)	0.13 (−0.12 to 0.37)	0.12 (−0.2 to 0.45)	0.1 (−0.14 to 0.35)	0.09 (−0.27 to 0.42)	0.02 (−0.3 to 0.34)	0.02 (−0.25 to 0.29)	0.01 (−0.34 to 0.35)	Quetiapine	—	0.88 (0.46 to 1.67)	0.93 (0.53 to 1.59)	0.18 (0.02 to 1.14)	0.54 (0.26 to 1.1)	0.49 (0.19 to 1.28)	**0.63 (0.41 to 0.94)**
0.35 (−0.33 to 1.02)	0.24 (−0.43 to 0.9)	0.18 (−0.48 to 0.83)	0.17 (−0.53 to 0.87)	0.15 (−0.51 to 0.82)	0.14 (−0.57 to 0.83)	0.07 (−0.64 to 0.78)	0.07 (−0.6 to 0.74)	0.06 (−0.64 to 0.75)	0.05 (−0.63 to 0.73)	Oxcarbazepine	—	—	—	—	—	—
0.31 (−0.02 to 0.63)	0.21 (−0.08 to 0.48)	0.15 (−0.14 to 0.43)	0.14 (−0.22 to 0.5)	0.12 (−0.17 to 0.42)	0.1 (−0.29 to 0.47)	0.04 (−0.35 to 0.42)	0.04 (−0.27 to 0.34)	0.02 (−0.35 to 0.4)	0.02 (−0.31 to 0.34)	−0.03 (−0.73 to 0.66)	Ziprasidone	1.06 (0.57 to 1.98)	0.21 (0.03 to 1.33)	0.61 (0.28 to 1.35)	0.56 (0.21 to 1.52)	0.71 (0.43 to 1.18)
0.23 (0.06 to 0.58)	0.22 (−0.02 to 0.43)	0.16 (−0.04 to 0.34)	0.15 (−0.16 to 0.45)	0.13 (−0.09 to 0.34)	0.12 (−0.22 to 0.42)	0.05 (−0.29 to 0.38)	0.05 (−0.2 to 0.29)	0.04 (−0.28 to 0.34)	0.03 (−0.24 to 0.29)	−0.02 (−0.65 to 0.6)	0.01 (−0.3 to 0.31)	Valproate	0.19 (0.03 to 1.21)	0.58 (0.29 to 1.16)	0.53 (0.2 to 1.36)	**0.67 (0.47 to 0.97)**
0.66 (−0.32 to 1.63)	0.56 (−0.42 to 1.51)	0.5 (−0.47 to 1.45)	0.49 (−0.5 to 1.47)	0.47 (−0.5 to 1.42)	0.45 (−0.55 to 1.43)	0.39 (−0.62 to 1.37)	0.39 (−0.59 to 1.35)	0.37 (−0.63 to 1.35)	0.37 (−0.61 to 1.33)	0.31 (−0.84 to 1.46)	0.35 (−0.64 to 1.32)	0.34 (−0.64 to 1.3)	Verapamil	2.99 (0.45 to 22.8)	2.72 (0.37 to 22.5)	3.46 (0.56 to 24.3)
0.51 (0.14 to 0.87)	**0.4 (0.06 to 0.72)**	**0.35 (0.02 to 0.66)**	0.34 (−0.06 to 0.72)	0.32 (0 to 0.63)	0.3 (−0.12 to 0.7)	0.24 (−0.18 to 0.64)	0.24 (−0.11 to 0.57)	0.22 (−0.19 to 0.61)	0.22 (−0.15 to 0.57)	0.16 (−0.55 to 0.87)	0.2 (−0.2 to 0.58)	0.19 (−0.15 to 0.52)	−0.15 (−1.15 to 0.85)	Lamotrigine	0.91 (0.31 to 2.61)	1.16 (0.64 to 2.1)
0.55 (0.07 to 1.04)	0.45 (−0.02 to 0.91)	0.39 (−0.07 to 0.85)	0.38 (−0.12 to 0.88)	0.36 (−0.1 to 0.83)	0.35 (−0.18 to 0.86)	0.28 (−0.24 to 0.81)	0.28 (−0.19 to 0.75)	0.27 (−0.25 to 0.78)	0.26 (−0.22 to 0.74)	0.21 (−0.57 to 0.99)	0.24 (−0.26 to 0.75)	0.23 (−0.23 to 0.7)	−0.11 (−1.14 to 0.94)	0.04 (−0.48 to 0.56)	Licarbazepine	1.27 (0.53 to 3.06)
0.65 (0.44 to 0.95)	**0.54 (0.36 to 0.7)**	**0.48 (0.34 to 0.62)**	**0.47 (0.22 to 0.73)**	**0.45 (0.3 to 0.61)**	**0.44 (0.15 to 0.71)**	**0.37 (0.06 to 0.65)**	**0.37 (0.2 to 0.55)**	**0.36 (0.06 to 0.63)**	**0.35 (0.14 to 0.55)**	0.3 (−0.35 to 0.95)	**0.33 (0.08 to 0.59)**	**0.32 (0.15 to 0.5)**	−0.02 (−0.96 to 0.94)	0.13 (−0.16 to 0.44)	0.09 (−0.34 to 0.53)	Placebo

Eficacia (crema) y descontinuación por cualquier causa (azul)

Yildiz A et al. Psychological Medicine 2015; 45:299–317

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Meta-análisis sobre el Uso de la Monoterapia de Eutimizantes en Depresión Bipolar - Respuesta

Treatments (trials)	Subjects (n)	Dropout (%) Drug/Placebo	Responders/Subjects		RR [95%CI]	
			Drug (%)	Placebo (%)		
Lithium						
Lithium [Li] (1)	265	25.0/27.8	85/136 (62.5)	72/129 (55.8)	1.12 [0.92–1.37]*	X
Anticonvulsants						
Carbamazepine [CBZ] (1)	70	26.5/40.0	30/47 (63.8)	8/23 (34.8)	1.84 [1.01–3.34]	
Lamotrigine [LTG] (5)	1071	34.8/33.6	255/541 (47.1)	160/530 (30.2)	1.56 [1.33–1.83]	
Valproate [VPA] (4)	140	41.1/47.9	28/69 (40.6)	13/71 (18.3)	2.22 [1.26–3.91]	
Anticonvulsants (10)	1281	34.1/40.5	313/657 (47.6)	181/624 (29.0)	1.61 [1.39–1.87]	
Antipsychotics						
Aripiprazole [APZ] (2)	690	44.0/32.4	148/337 (43.9)	147/353 (41.6)	1.10 [0.81–1.48]*	X
Cariprazine[CAR] (1)	236	29.1/28.0	86/191 (44.4)	14/45 (31.1)	1.81 [0.91–3.62]*	
Lurasidone [LUR] (1)	485	–	168/323 (52.0)	49/162 (30.2)	2.50 [1.68–3.73]	
Olanzapine [ONZ] (2)	1220	36.9/45.0	317/694 (45.7)	185/526 (35.2)	→ 1.55 [1.23–1.96]	
Quetiapine [QTP] (5)	2485	34.4/35.1	1135/1760 (64.5)	322/725 (44.4)	2.27 [1.91–2.71]	
Ziprasidone [ZPS] (2)	928	38.8/31.9	281/554 (50.7)	187/374 (50.0)	1.03 [0.79–1.34]*	X
Antipsychotics (13)	6044	36.6/35.1	2135/3859 (55.3)	904/2185 (41.4)	1.28 [1.09–1.51]	
Pooled/totals (24)	7590	35.7/39.9	2533/4652 (54.4)	1157/2938 (39.4)	1.34 [1.17–1.53]	

Baldessarini RJ et al. Mol Psychiatry 2019;24:198-217

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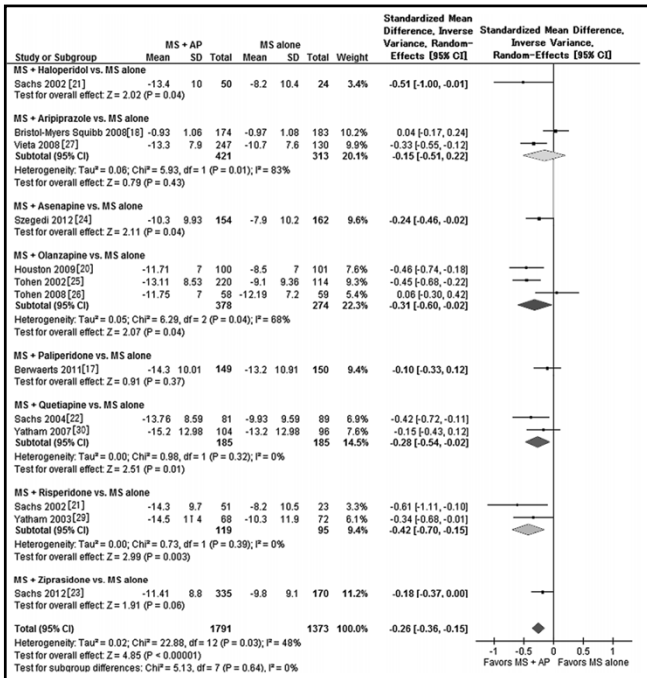

Study or Subgroup	MS + AP Mean	SD	Total	MS alone Mean	SD	Total	Weight	Standardized Mean Difference, Inverse Variance, Random–Effects [95% CI]
MS + Haloperidol vs. MS alone								
Sachs 2002 [21]	-13.4	10	50	-8.2	10.4	24	3.4%	-0.51 [-1.00, -0.01]
Test for overall effect: Z = 2.02 (P = 0.04)								
MS + Aripiprazole vs. MS alone								
Bristol-Myers Squibb 2008[18]	-0.93	1.06	174	-0.97	1.08	183	10.2%	0.04 [-0.17, 0.24]
Vieta 2008 [27]	-13.3	7.9	247	-10.7	7.6	130	9.9%	-0.33 [-0.55, -0.12]
Subtotal (95% CI)			421			313	20.1%	-0.15 [-0.51, 0.22]
Heterogeneity: Tau² = 0.06; Chi² = 5.93, df = 1 (P = 0.01); I² = 83%								
Test for overall effect: Z = 0.79 (P = 0.43)								
MS + Asenapine vs. MS alone								
Szegedi 2012 [24]	-10.3	9.93	154	-7.9	10.2	162	9.6%	-0.24 [-0.46, -0.02]
Test for overall effect: Z = 2.11 (P = 0.04)								
MS + Olanzapine vs. MS alone								
Houston 2009[20]	-11.71	7	100	-8.5	7	101	7.6%	-0.46 [-0.74, -0.18]
Tohen 2002[25]	-13.11	8.53	220	-9.1	9.36	114	9.3%	-0.45 [-0.68, -0.22]
Tohen 2008 [26]	-11.75	7	58	-12.19	7.2	59	5.4%	0.06 [-0.30, 0.42]
Subtotal (95% CI)			378			274	22.3%	-0.31 [-0.60, -0.02]
Heterogeneity: Tau² = 0.05; Chi² = 6.29, df = 2 (P = 0.04); I² = 68%								
Test for overall effect: Z = 2.07 (P = 0.04)								
MS + Paliperidone vs. MS alone								
Berwaerts 2011[17]	-14.3	10.01	149	-13.2	10.91	150	9.4%	-0.10 [-0.33, 0.12]
Test for overall effect: Z = 0.91 (P = 0.37)								
MS + Quetiapine vs. MS alone								
Sachs 2004[22]	-13.76	8.59	81	-9.93	9.59	89	6.9%	-0.42 [-0.72, -0.11]
Yatham 2007[30]	-15.2	12.98	104	-13.2	12.98	96	7.6%	-0.15 [-0.43, 0.12]
Subtotal (95% CI)			185			185	14.5%	-0.28 [-0.54, -0.02]
Heterogeneity: Tau² = 0.00; Chi² = 0.98, df = 1 (P = 0.32); I² = 0%								
Test for overall effect: Z = 2.51 (P = 0.01)								
MS + Risperidone vs. MS alone								
Sachs 2002 [21]	-14.3	9.7	51	-8.2	10.5	23	3.3%	-0.61 [-1.11, -0.10]
Yatham 2003[29]	-14.5	11.4	68	-10.3	11.9	72	6.1%	-0.34 [-0.68, -0.01]
Subtotal (95% CI)			119			95	9.4%	-0.42 [-0.70, -0.15]
Heterogeneity: Tau² = 0.00; Chi² = 0.73, df = 1 (P = 0.39); I² = 0%								
Test for overall effect: Z = 2.99 (P = 0.003)								
MS + Ziprasidone vs. MS alone								
Sachs 2012[23]	-11.41	8.8	335	-9.8	9.1	170	11.2%	-0.18 [-0.37, 0.00]
Test for overall effect: Z = 1.91 (P = 0.06)								
Total (95% CI)			1791			1373	100.0%	-0.26 [-0.36, -0.15]
Heterogeneity: Tau² = 0.02; Chi² = 22.88, df = 12 (P = 0.03); I² = 48%								
Test for overall effect: Z = 4.85 (P < 0.00001)								
Test for subgroup differences: Chi² = 5.13, df = 7 (P = 0.64), I² = 0%								

Reducción en Severidad de Síntomas maníacos (Terapia Combinada vs Monoterapia – 3 Sem)

Retiro del estudio por cualquier motivo
MS + AP vs. MS: RR=0.99, 0.88-1.12
MS + AP vs. AP: RR 0.70, 0.47- 1.04

Retiro por EAs
MS + AP vs. MS: RR=1.39, 0.97-1.99
MS + AP vs. AP: RR=0.62, 0.27-1.40
(la terapia de combinación se asoció con más somnolencia)

Actualmente no hay pruebas sólidas para juzgar si la terapia de combinación de EM y AP es más eficaz que la monoterapia de EM como la terapia inicial para pacientes con manía aguda sin medicación previa

Ogawa Y et al. CNS *Drugs 2014;28:989–1003*

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Agent(s)	Study: Author, year, reference number	Study: Method	Definitions of mixed mania/hypomania	Efficacy (improvement in): Manic/ hypomanic symptoms	Efficacy (improvement in): Depressive symptoms
Mixed mania					
Atypical antipsychotics					
ARP	Sachs *et al.*, 2006[7]	Subgroup analysis	Mixed episode (DSM–IV)	>PLA	>PLA
	Suppes *et al.*, 2008[8]	Pooled analysis	Manic/mixed episodes (DSM–IV) with MADRS scores >9	>PLA	NR
ASE	McIntyre *et al.*, 2009[10]	Subgroup analysis	Mixed episode (DSM–IV)	=PLA	NR
	Szegedi *et al.*, 2011[12]	Pooled analysis	Population 1, manic/mixed episodes (DSM–IV) with MADRS scores ≥20; population 2, manic/mixed episodes (DSM–IV) with CGI–BP–D scale severity scores ≥4; population 3, mixed episode (DSM–IV)	NR	>PLA
	Azorin *et al.*, 2013[13]	Pooled analysis	Mixed episode (DSM–IV)	>PLA	>PLA
	McIntyre *et al.*, 2013[14]	Pooled analysis	Manic episode with mixed features (DSM–5)	>PLA	>PLA
OLA	Tohen *et al.*, 1999[35]	Subgroup analysis	Manic/mixed episodes (DSM–IV) with HAMD–21 scores ≥20	>PLA	Not worsened
	Tohen *et al.*, 2000[15]	Subgroup analysis	Mixed episode (DSM–IV)	>PLA	>PLA
	Baker *et al.*, 2003[17]	Pooled analysis	Manic/mixed episodes (DSM–IV) with HAMD–21 scores ≥20	>PLA	>PLA
	Baldessarini *et al.*, 2003[18]	Pooled analysis	Mixed episode (DSM–IV)	>PLA	NR
	McIntyre *et al.*, 2009[10]	Subgroup analysis	Mixed episode (DSM–IV)	>PLA	NR
	Szegedi *et al.*, 2011[12]	Pooled analysis	Population 1, manic/mixed episodes (DSM–IV) with MADRS scores ≥20; population 2, manic/mixed episodes (DSM–IV) with CGI–BP–D scale severity scores ≥4; population 3, mixed episode (DSM–IV)	NR	>PLA
	Azorin *et al.*, 2013[13]	Pooled analysis	Mixed episode (DSM–IV)	=PLA	=PLA
	McIntyre *et al.*, 2013[14]	Pooled analysis	Manic episode with mixed features (DSM–5)	>PLA	>PLA
	Tohen *et al.*, 2014[19]	Pooled analysis	Manic episode with mixed features (DSM–5)	>PLA	=PLA
PAL–ER	Vieta *et al.*, 2010[21]	Subgroup analysis	Mixed episode (DSM–IV)	>PLA	NR
	Berwaerts *et al.*, 2013[22]	Subgroup analysis	Mixed episode (DSM–IV)	>PLA	NR
QUE–XR	Cutler *et al.*, 2011[23]	Subgroup analysis	Mixed episode (DSM–IV)	=PLA	=PLA
ZIP	Keck *et al.*, 2003[24]	Subgroup analysis	Mixed episode (DSM–IV)	>PLA	NR
	Stahl *et al.*, 2010[26]	Pooled analysis	Manic/mixed episodes (DSM–IV) with scores ≥2 on at least 2 of the 8 selected HAMD items	>PLA	>PLA
Mood stabilizers					
CBZ–ERC	Weisler *et al.*, 2004[27]	Subgroup analysis	Mixed episode (DSM–IV)	>PLA	>PLA
	Weisler *et al.*, 2005[28]	Subgroup analysis	Mixed episode (DSM–IV)	>PLA	=PLA
	Weisler *et al.*, 2006[29]	Pooled analysis	Mixed episode (DSM–IV)	>PLA	>PLA
LI	Swann *et al.*, 1997[31]	Subgroup analysis	Mania (RDC) with significant depressive symptoms defined by SADS–C depression subscale and ADRS	=PLA	NR
DVP	Swann *et al.*, 1997[31]	Subgroup analysis	Mania (RDC) with significant depressive symptoms defined by SADS–C depression subscale and ADRS	>PLA	NR
	Bowden *et al.*, 2006[32]	Subgroup analysis	Mixed episode (DSM–IV–TR)	>PLA	NR
Combination					
OLA + LI/VAL	Tohen *et al.*, 2002[33]	Subgroup analysis	Mixed episode (DSM–IV) with HAMD–21 scores ≥20	>PLA + LI/VAL	>PLA + LI/VAL
	Baker *et al.*, 2004[34]	Subgroup analysis	Manic/mixed episodes (DSM–IV) with HAMD–21 scores ≥20	>PLA + LI/VAL	>PLA + LI/VAL
OLA + VAL	Houston *et al.*, 2009[35]	Prospective	Mixed episode (DSM–IV–TR)	>PLA + VAL	>PLA + VAL
Mixed hypomania					
QUE	Suppes *et al.*, 2013[47]	Prospective	BD–II (DSM–IV–TR) with YMRS scores ≥12 and MADRS scores ≥15	=PLA	>PLA
				>PLA, overall severity & functioning*	

Manía con Síntomas Mixtos. Mejoría con Eutimizantes

Aripiprazol, asenapina, carbamazepina, olanzapina y ziprasidona mostraron la mayor evidencia de eficacia en el tratamiento de fase aguda de pacientes bipolares con síntomas mixtos.

Las terapias de combinación con olanzapina y estabilizadores del estado de ánimo pueden considerarse en casos graves.

Takeshima M. CNS Spectr 2017;22:177-185

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Profilaxis Farmacológica en Trastorno Bipolar I

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Meta-Análisis: Riesgo de Recurrencia Luego de un Episodio Maníaco o Mixto

- En los estudios en adultos, el 35% (30-41%) experimentaron recurrencia después de la recuperación dentro de 1 año, el 59% después de 2 años y el 58% después de 4 años, respectivamente.
- En los estudios en niños y adolescentes, el 48% (38-58%) experimentaron recurrencia después de la recuperación dentro de 1 año, el 30% y el 60% después de 2 años y el 64% y el 67% después de 4 a 5 años, respectivamente.

Kessing LV et al. Bipolar Disord 2018;20:9-17

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Predictores Individuales de Recurrencias en Trastorno Bipolar (STEP-BD)

Feature	Depressive Recurrence Hazard Ratio	Depressive Recurrence 95% CI	Manic/Hypomanic/Mixed Recurrence Hazard Ratio	Manic/Hypomanic/Mixed Recurrence 95% CI
Lifetime mania phases (≥20 versus <5)			1.552	1.068–2.253
Lifetime depression phases (≥20 versus <5)	1.304	1.026–1.657		
Current anxiety disorder	1.322	1.043–1.676		
Current substance use disorder			1.613	1.011–2.573
Lifetime eating disorders	1.650	1.129–2.411		
Number of residual depressive symptoms at recovery	1.143	1.084–1.206		
Number of residual manic symptoms at recovery	1.204	1.097–1.322	1.316	1.153–1.503
Male gender	0.735	0.578–0.935		
Bipolar I type			1.646	1.017–2.664
Rapid cycling, past year	1.366	1.051–1.776	1.852	1.258–2.726
Number of episodes of depression, past year			1.053	1.019–1.089

Perlis RH et al. Am J Psychiatry. 2006;163:217-224

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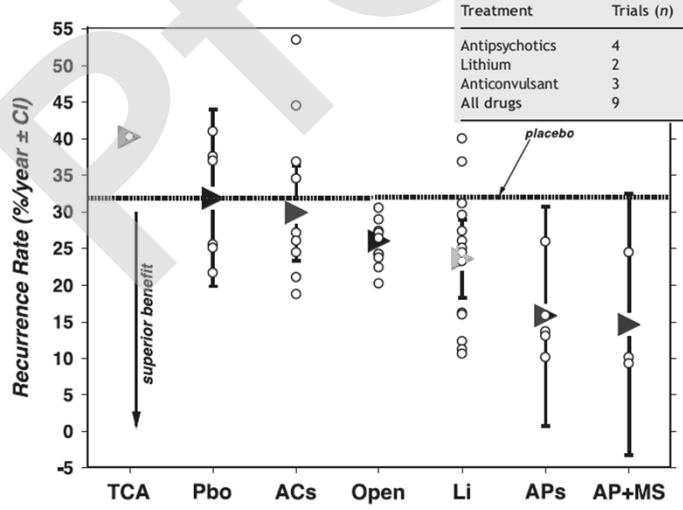
Eutimizantes en Profilaxis. Meta-Análisis

Treatment	Trials (*n*)	Subjects (*N*)	RR [95% CI]	NNT [95% CI]
Antipsychotics	4	996	0.56[0.092-0.45]	4.3[3.3-6.1]
Lithium	2	1123	0.62[0.42-0.91]	4.9[3.1-11]
Anticonvulsant	3	463	0.87[0.73-1.0]	13[6.0-56]
All drugs	9	2582	0.63[0.51-0.77]	5.1[3.8-7.7]



Tasas de recurrencia en trastorno bipolar

Vazquez GH et al. Eur Neuropsychopharmacol 2015;25:1501-12

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Eutimizantes en Prevención de Recurrencias en General y Tolerabilidad. Meta-Análisis de Red

Tolerability (discontinuation due to adverse event; 95% CrI) Comparison Efficacy (any mood episode relapse; 95% CrI)

ARP+VPA	0·04 (0·00–1·64)	0·07 (0·00–2·01)	0·13 (0·00–3·56)	0·04 (0·00–1·01)	0·15 (0·00–5·77)	0·02 (0·00–1·88)	0·06 (0·00–1·49)	0·04 (0·00–1·69)	0·12 (0·01–2·40)	0·09 (0·00–2·87)	0·04 (0·00–1·33)	0·23 (0·01–7·41)	0·14 (0·00–4·88)	0·06 (0·00–9·80)	0·16 (0·00–4·28)
0·71 (0·22–2·27)	LIT+OXC	1·82 (0·24–12·20)	3·24 (0·44–23·26)	0·97 (0·11–8·77)	3·80 (0·33–44·39)	0·45 (0·01–19·81)	1·54 (0·26–9·16)	0·85 (0·05–13·79)	2·95 (0·34–25·00)	2·23 (0·24–19·23)	1·10 (0·14–8·78)	5·78 (0·65–50·00)	3·37 (0·29–40·00)	1·41 (0·02 to 134·69)	3·98 (0·60–27·00)
0·58 (0·22–1·55)	0·81 (0·40–1·63)	OLZ	1·78 (0·64–6·13)	0·53 (0·13–2·67)	2·08 (0·35–13·89)	0·25 (0·01–7·58)	0·84 (0·40–2·19)	0·47 (0·05–4·43)	1·62 (0·42–7·58)	1·22 (0·36–4·55)	0·61 (0·17–2·47)	3·17 (0·84–13·63)	1·85 (0·33–11·76)	0·77 (0·01–48·91)	2·18 (0·95–6·13)
0·55 (0·20–1·49)	0·77 (0·38–1·57)	0·96 (0·66–1·34)	QTP	0·30 (0·07–1·38)	1·17 (0·18–7·13)	0·14 (0·00–4·24)	0·48 (0·19–1·14)	0·26 (0·03–2·25)	0·91 (0·21–4·02)	0·69 (0·16–2·79)	0·34 (0·09–1·34)	1·78 (0·44–6·99)	1·04 (0·19–5·71)	0·44 (0·01–27·06)	1·23 (0·57–2·73)
0·55 (0·20–1·49)	0·77 (0·37–1·64)	0·96 (0·62–1·48)	1·00 (0·64–1·60)	LIT+VPA	3·91 (0·45–31·69)	0·46 (0·01–16·35)	1·58 (0·45–5·37)	0·88 (0·08–10·06)	3·03 (0·83–11·11)	2·29 (0·36–13·51)	1·14 (0·22–5·61)	5·95 (1·02–33·33)	3·46 (0·43–27·78)	1·45 (0·02–>100)	4·09 (1·01–16·96)
0·55 (0·18–1·62)	0·76 (0·33–1·77)	0·95 (0·54–1·66)	0·99 (0·56–1·77)	0·99 (0·52–1·86)	ARP+LTG	0·12 (0·00–5·05)	0·41 (0·07–2·24)	0·22 (0·02–3·13)	0·78 (0·10–6·29)	0·59 (0·08–4·41)	0·29 (0·04–2·17)	1·52 (0·47–5·13)	0·89 (0·09–8·70)	0·37 (0·00–31·25)	1·05 (0·20–5·84)
0·46 (0·16–1·32)	0·65 (0·30–1·41)	0·81 (0·49–1·30)	0·84 (0·51–1·39)	0·84 (0·48–1·44)	0·85 (0·43–1·65)	LIT+IMP	3·41 (0·12–89·12)	1·89 (0·04–94·44)	6·54 (0·20–>100)	4·95 (0·15–>100)	2·45 (0·07–73·77)	12·82 (0·37–>100)	7·46 (0·18–>100)	3·13 (0·10–84·61)	8·82 (0·31–>100)
0·47 (0·18–1·21)	0·65 (0·34–1·26)	0·81 (0·62–1·03)	0·84 (0·64–1·13)	0·84 (0·58–1·21)	0·85 (0·51–1·44)	1·00 (0·66–1·53)	LIT	0·55 (0·07–4·64)	1·92 (0·60–6·37)	1·45 (0·39–5·32)	0·72 (0·25–2·04)	3·76 (1·13–12·66)	2·19 (0·41–11·90)	0·92 (0·02–54·05)	2·58 (1·33–5·39)
0·46 (0·16–1·36)	0·65 (0·28–1·49)	0·80 (0·46–1·38)	0·84 (0·48–1·46)	0·84 (0·44–1·56)	0·85 (0·41–1·70)	1·00 (0·52–1·93)	0·99 (0·59–1·66)	ARP	3·46 (0·30–38·46)	2·62 (0·23–29·41)	1·30 (0·12–13·89)	6·80 (0·65–66·67)	3·95 (0·33–47·62)	1·66 (0·02–>100)	4·67 (0·64–34·26)
0·46 (0·18–1·16)	0·64 (0·32–1·29)	0·79 (0·56–1·13)	0·83 (0·58–1·23)	0·83 (0·58–1·19)	0·84 (0·47–1·50)	0·98 (0·61–1·62)	0·98 (0·77–1·28)	0·99 (0·56–1·78)	VPA	0·76 (0·12–4·29)	0·38 (0·08–1·79)	1·96 (0·36–10·76)	1·14 (0·14–8·79)	0·48 (0·01–34·54)	1·35 (0·35–5·32)
0·45 (0·17–1·24)	0·63 (0·31–1·32)	0·79 (0·55–1·10)	0·82 (0·56–1·22)	0·82 (0·50–1·32)	0·83 (0·46–1·49)	0·98 (0·58–1·64)	0·97 (0·70–1·34)	0·98 (0·55–1·75)	0·99 (0·66–1·47)	RisLAI	0·50 (0·09–2·66)	2·59 (0·50–14·15)	1·51 (0·22–11·13)	0·63 (0·01–42·48)	1·78 (0·54–6·41)
0·43 (0·15–1·22)	0·60 (0·27–1·30)	0·74 (0·45–1·19)	0·77 (0·46–1·27)	0·77 (0·44–1·32)	0·78 (0·40–1·51)	0·92 (0·51–1·65)	0·91 (0·60–1·38)	0·92 (0·47–1·78)	0·93 (0·56–1·51)	0·94 (0·55–1·57)	CBZ	5·24 (1·07–26·32)	3·05 (0·44–21·74)	1·28 (0·02–83·33)	3·60 (1·04–12·94)
0·38 (0·14–1·01)	0·53 (0·27–1·06)	0·66 (0·48–0·89)	0·69 (0·50–0·96)	0·68 (0·44–1·04)	0·69 (0·43–1·10)	0·81 (0·51–1·31)	0·81 (0·64–1·02)	0·82 (0·47–1·41)	0·83 (0·59–1·15)	0·83 (0·59–1·19)	0·89 (0·56–1·44)	LTG	0·58 (0·08–4·20)	0·24 (0·00–17·78)	0·69 (0·21–2·35)
0·34 (0·12–0·99)	0·48 (0·22–1·05)	0·60 (0·37–0·94)	0·63 (0·39–1·01)	0·62 (0·36–1·08)	0·63 (0·33–1·20)	0·74 (0·42–1·34)	0·74 (0·48–1·13)	0·75 (0·39–1·41)	0·76 (0·46–1·22)	0·76 (0·47–1·25)	0·81 (0·45–1·47)	0·91 (0·58–1·43)	PAL	0·42 (0·01–31·12)	1·18 (0·26–5·47)
0·30 (0·11–0·84)	0·43 (0·20–0·89)	0·53 (0·34–0·80)	0·55 (0·36–0·86)	0·55 (0·33–0·90)	0·56 (0·30–1·03)	0·66 (0·43–1·00)	0·65 (0·46–0·92)	0·66 (0·36–1·21)	0·67 (0·43–1·01)	0·67 (0·42–1·06)	0·72 (0·42–1·23)	0·80 (0·54–1·20)	0·88 (0·51–1·50)	IMP	2·82 (0·05–>100)
0·29 (0·11–0·76)	0·40 (0·21–0·79)	0·50 (0·39–0·63)	0·52 (0·40–0·68)	0·52 (0·35–0·77)	0·53 (0·32–0·88)	0·62 (0·40–0·96)	0·62 (0·53–0·72)	0·62 (0·38–1·03)	0·63 (0·47–0·83)	0·64 (0·48–0·85)	0·68 (0·44–1·06)	0·76 (0·62–0·94)	0·84 (0·56–1·24)	0·95 (0·66–1·36)	PLB

Miura T et al. Lancet Psychiatry 2014;1: 351–59

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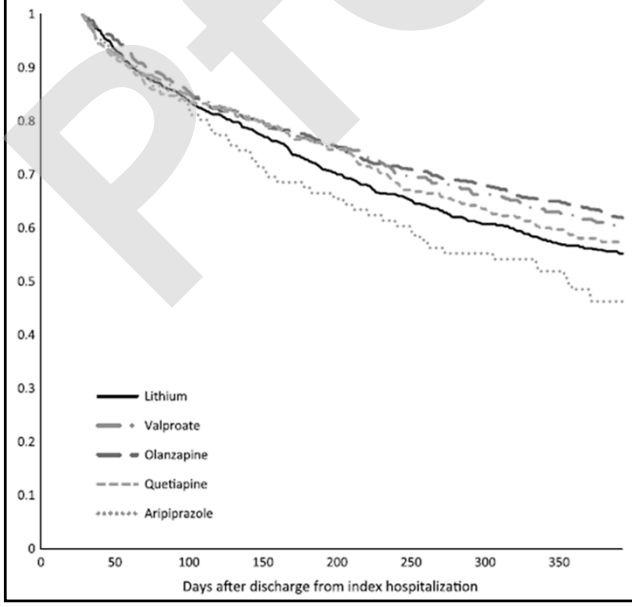
Estudio Sueco (n = 6502). Reducción de Rehospitalización



Las tasas de rehospitalización al cabo de un año fueron del 39% en aquellos que iniciaron tratamiento profiláctico vs. 46% en los que no lo iniciaron.
Las terapias combinadas se asociaron a menor riesgo de rehospitalización (<34%)

Wingård L et al. J Affect Disord 2017; 217 :16–23

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Tasas de Recurrencias en Trastorno Bipolar: Estudios Naturalísticos vs. ECAs

Characteristic	Naturalistic	Controlled	*p*-value (*t*-score)
Drug-treated groups (*n*)[a]	10	31	-
Subjects (*N*)	3904	4828	-
Onset age (yrs)	29.1±8.30	23.1±8.97	0.15 (1.49)
Intake age (yrs)	43.2±4.17	34.8±12.0	0.08 (1.87)
Women (%)	53.3±10.5	50.9±6.33	0.56 (0.35)
Bipolar-I (%)	85.8±16.4	96.0±8.09	0.08 (1.84)
Ever rapid-cycling (%)	21.5±16.3	32.0±16.5	0.27 (1.14)
Initially depressed (%)	69.6±25.0	0.00±0.00	0.005 (4.71)
First recurrence depression (%)	55.7±15.4	51.5±14.5	0.55 (0.74)
Years followed	2.06±0.18	1.77±0.26	0.01 (2.71)
Dropout rate, drugs (%)[a]	20.9±14.0	33.2±12.8	0.01 (2.58)
Recurrence risk, drugs (%/yr)[a]	26.3±3.14	21.9±2.70	0.50 (0.68)

[a]Placebo arms of controlled trials not included.

Vazquez GH et al. Eur Neuropsychopharmacol 2015;25:1501-12

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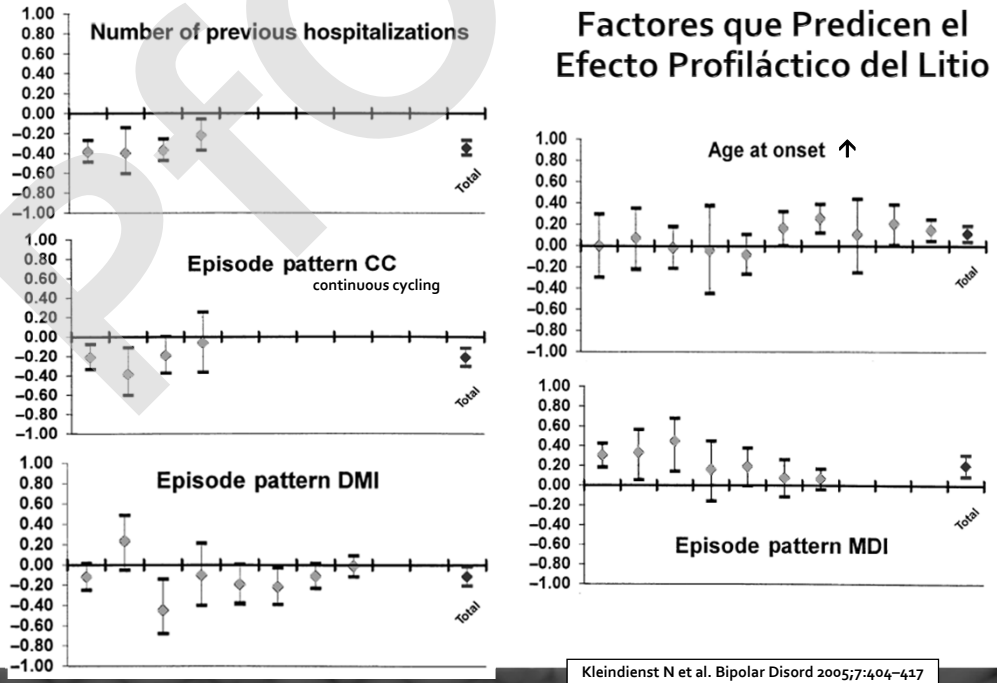
Factores que Predicen el Efecto Profiláctico del Litio



Kleindienst N et al. Bipolar Disord 2005;7:404–417

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Prevención de Recurrencias en Pacientes con Ciclado Rápido

Tratamiento	n	Duración	Prevención	Conversiones
Aripiprazol	28	100 sem.	ARI > PLA	?
Olanzapina	90	52 sem	NRC > RC (OLZ>PLA)	RC > NRC
Quetiapina	38	52 sem.	QUE > DIV (depr.)	NS
Carbamazepina	52	52 sem.	Li+CBZ > Li > CBZ	?
Lamotrigina	177	52 sem.	LTG > PLA (BPII)	?
Litio	31	26 sem.	Li = Li+DIV	?
Litio	60	140 sem.	Li = DIV	?

Conclusión:
La eficacia de aripiprazol y olanzapina en pacientes con ciclado rápido parece ir más allá de la fase aguda. La quetiapina y la lamotrigina parecen prevenir recurrencias depresivas en ciclatores rápidos

Fountoulakis KN et al. Bipolar Disord 2013;15:115–137

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Manía con Síntomas Mixtos. Profilaxis con Eutimizantes

Agent(s)	Study: Author, year, reference number	Study: Method	Definitions of mixed mania	Efficacy (time to relapse into): Manic episode	Efficacy (time to relapse into): Depressive episode
Atypical antipsychotics					
OLA	Tohen *et al.*, 2006[36]	Subgroup analysis	Mixed episode (DSM–IV)	>PLA, any mood episode	
	Tohen *et al.*, 2009[37]	Subgroup analysis	Mixed episode (DSM–IV)	>PLA	>PLA
QUE	Weisler *et al.*, 2011[38]	Subgroup analysis	Mixed episode (DSM–IV)	>PLA	>PLA
Mood stabilizers					
LI	Bowden *et al.*, 2005[39]	Subgroup analysis	Manic episode (DSM–III–R) with significant depressive symptoms defined by SADS-C depression subscale	=PLA	=PLA
	Weisler *et al.*, 2011[38]	Subgroup analysis	Mixed episode (DSM–IV)	>PLA	=PLA
DVP	Bowden *et al.*, 2005[39]	Subgroup analysis	Manic episode (DSM–III–R) with significant depressive symptoms defined by the SADS–C depression subscale	=PLA	=PLA
Combination					
ARP + LTG	Carlson *et al.*, 2012[41]	Subgroup analysis	Mixed episode (DSM–IV–TR)	NR	>PLA + LTG
ARP + LI/VAL	Yatham *et al.*, 2013[43]	Subgroup analysis	Mixed episode (DSM–IV–TR)	>PLA*	=PLA
QUE + DVP/LI	Vieta *et al.*, 2008[45]	Subgroup analysis	Mixed episode (DSM–IV)	>PLA + DVP/LI	>PLA + DVP/LI
	Suppes *et al.*, 2009[44]	Subgroup analysis	Mixed episode (DSM–IV)	>PLA + DVP/LI	>PLA + DVP/LI
	Vieta *et al.*, 2012[46]	Pooled analysis	Mixed episode (DSM–IV)	>PLA + DVP/LI	>PLA + DVP/LI

Takeshima M. CNS Spectr 2017;22:177-185

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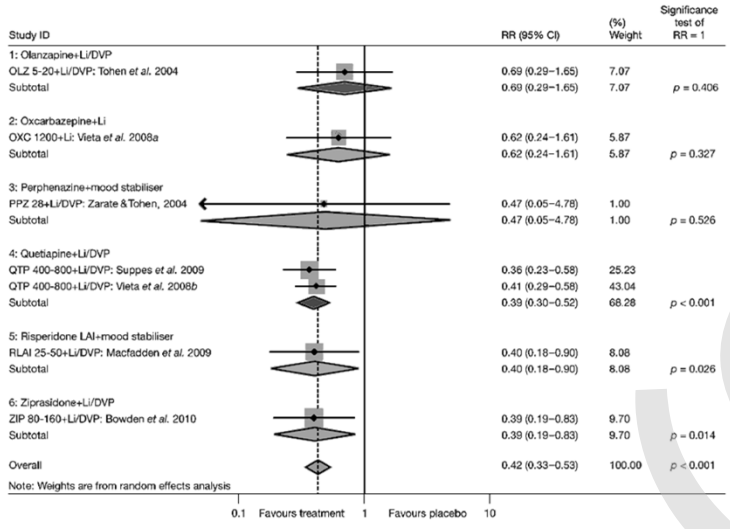
Terapia Combinada Versus Monoterapia en Prevención de Recurrencias Manícas en TB (Estudios Enriquecidos)[1]



Aripiprazol+Li/DVP:[2]
HR = 0.35 (0.15–0.83)

1. Vieta E et al. Int J Neuropsychopharmacol 2011;14:1029-1049; 2. Marcus R et al. Bipolar Disord 2011;13:133–144

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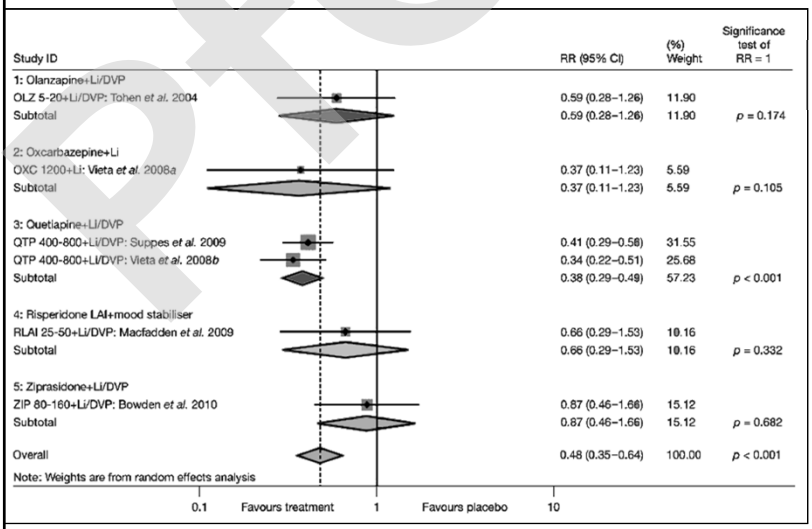
Terapia Combinada Versus Monoterapia en Prevención de Recurrencias Depresivas en TB (Estudios Enriquecidos)



Aripiprazol+Li/DVP:[2]
HR = 0.73 (0.36–1.48)

1. Vieta E et al. Int J Neuropsychopharmacol 2011;14:1029-1049; 2. Marcus R et al. Bipolar Disord 2011;13:133–144

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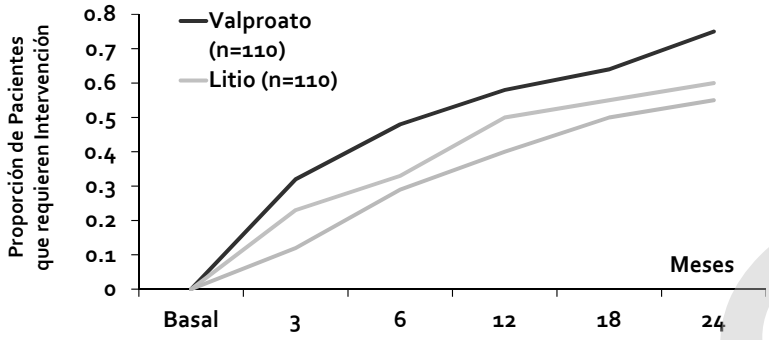
Combinación Estabilizadores vs. Monoterapia a Dos Años: Estudio BALANCE



La terapia combinada de Litio + Valproato fue más eficaz que la monoterapia con valproato (RR=0.78; 0.63-0.96)[2]

	Meses	IC 95%
Li + VPA	15.5	10.4 - **
Li	10.5	7.7-18.3
VPA	7.1	4.6-12.2

	HR	IC 95%	Valor p
Li + VPA vs. Li	0.82	[0.58-1.17]	.27
Li + VPA vs. VPA	0.59	[0.42-0.83]	0.002
Li vs. VPA	0.71	[0.51-1.00]	0.047

1. Geddes JR et al. Lancet 2010; 375: 385–95; 2. Cipriani A et al. Cochrane Database Syst Rev 2013 Oct 17;(10):CD003196

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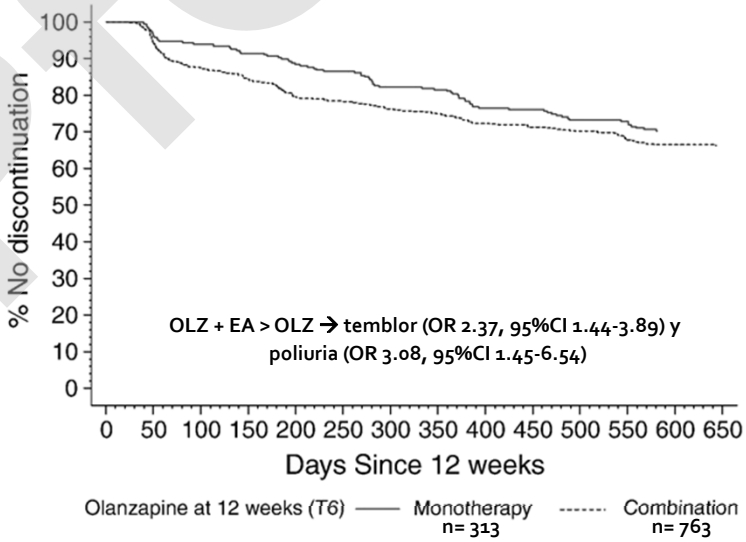
Olanzapina Monoterapia Vs. Olanzapina + Estabilizador del Ánimo (Estudio EMBLEM)



OLZ + EA > OLZ → temblor (OR 2.37, 95%CI 1.44-3.89) y poliuria (OR 3.08, 95%CI 1.45-6.54)

Gonzalez-Pinto A et al. J Affect Disord 2011;131:320-329

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Eventos Adversos Comunes con el Uso de Eutimizantes

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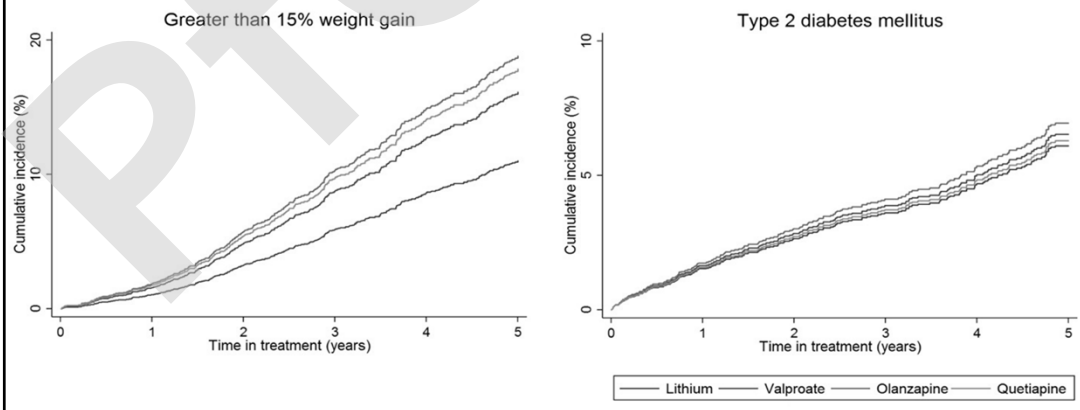
Cambios Metabólicos con Eutimizantes (Estudio Naturalístico)



estudio de cohortes:	litio (n = 2148),	valproato (n = 1670),	olanzapina (n = 1477) o	quetiapina (n = 1376)
Ganancia de peso - aHR (95%CI):	1	1.62 (1.31–2.01)	1.84 (1.47–2.30)	1.67 (1.24–2.20)
Diabetes tipo 2 - aHR (95%CI):	1	1.08 (0.83–1.42)	1.20 (0.89–1.61)	0.94 (0.65–1.35)

Hayes JF et al. PLoS Med 2016;13(8): e1002058

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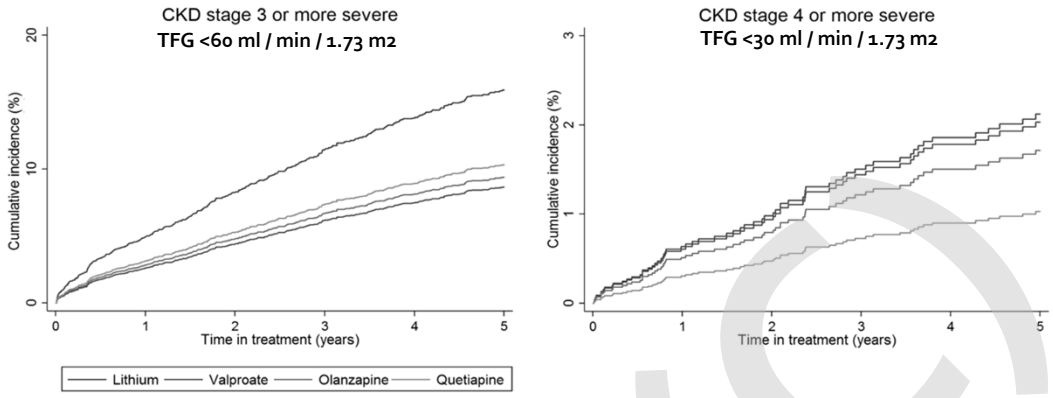
Alteración en Función Renal con Eutimizantes



estudio de cohortes: litio (n = 2148), valproato (n = 1670), olanzapina (n = 1477) o quetiapina (n = 1376)

CKD 3 - aHR (95%CI):	1	0.56 (0.45–0.69)	0.57 (0.45–0.71)	0.62 (0.47–0.80)
CKD 4 - aHR (95%CI):	1	0.94 (0.59–1.50)	0.65 (0.37–1.12)	0.67 (0.33–1.37)

Hayes JF et al. PLoS Med 2016;13(8): e1002058

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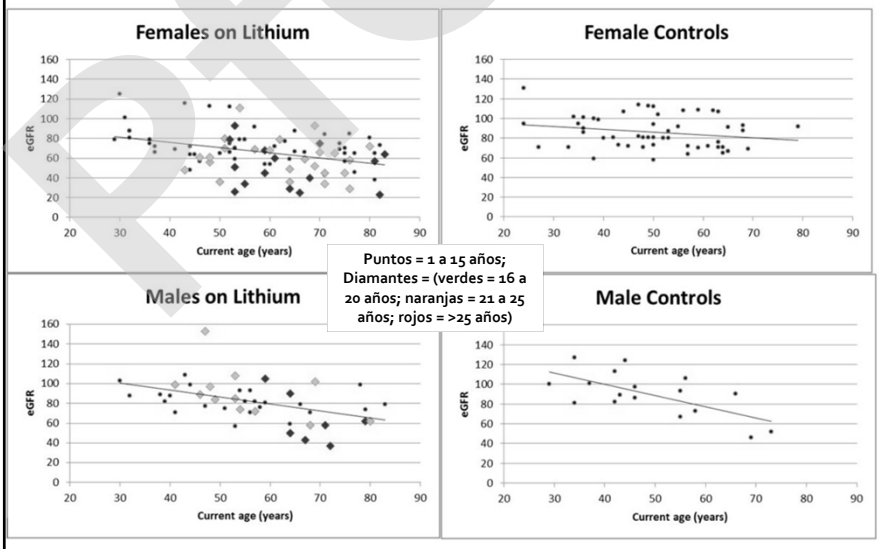
La Disminución en la Tasa de Filtración Glomerular (eGFR) con Litio Depende del Tiempo de Tratamiento



Puntos = 1 a 15 años; Diamantes = (verdes = 16 a 20 años; naranjas = 21 a 25 años; rojos = >25 años)

eGFRs < 60 ml/min fue más común en ptes tratados con Li+ (38/139 = 27.3%) vs. otros (4/70 = 5.7%) (P=0.0002).

Análisis de regresión muestran mayor impacto en la eGFR con la edad, el género femenino y la duración del tto

Bocchetta A et al. BMC Medicine 2013;11:33

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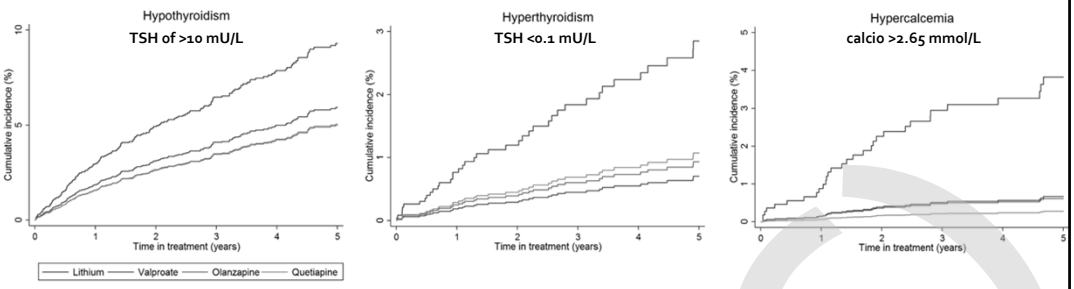
Alteraciones en Función Tiroidea con Eutimizantes



estudio de cohortes:	**litio (n = 2148)**	**valproato (n = 1670)**	**olanzapina (n = 1477)**	**o quetiapina (n = 1376)**
Hipotiroidismo - aHR (95%CI):	**1**	**0.60 (0.40–0.89)**	**0.48 (0.29–0.77)**	**0.63 (0.38–1.05)**
Hipertiroidismo - aHR (95%CI):	**1**	**0.24 (0.09–0.61)**	**0.31 (0.13–0.73)**	**0.45 (0.18–1.18)**
Hipercalcemia - aHR (95%CI):	**1**	**0.25 (0.10–0.60)**	**0.32 (0.14–0.76)**	**0.23 (0.07–0.73)**

Hayes JF et al. PLoS Med 2016;13(8): e1002058

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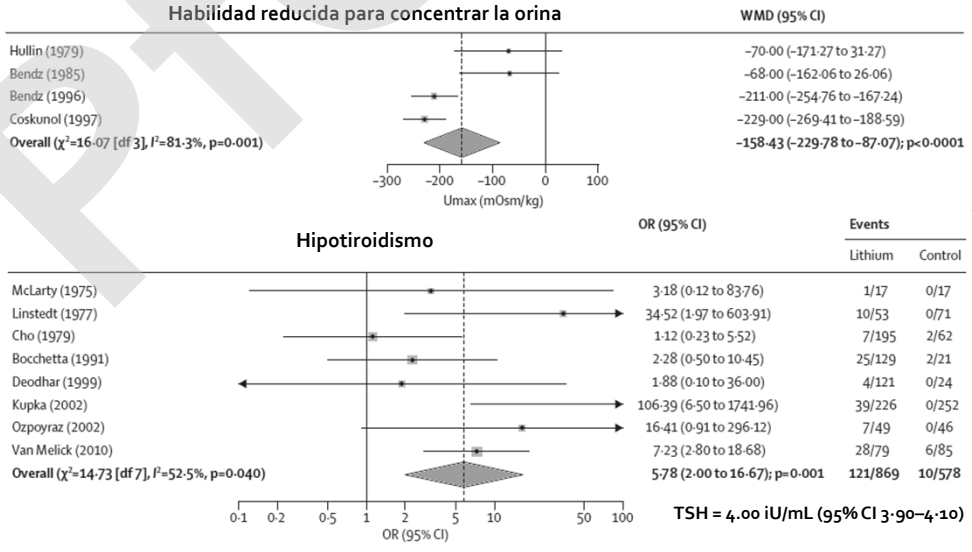
Toxicidad del Litio a Largo Plazo



McKnight RF et al. Lancet 2012;379:721–728

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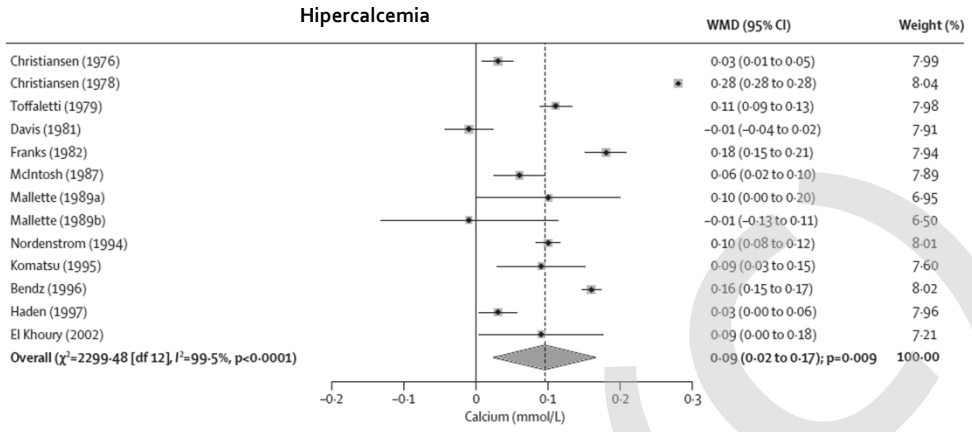
Toxicidad del Litio a Largo Plazo



TFG, TSH y calcio deben ser medidos al menos cada 12 meses

Hormona paratiroidea = +7·32 pg/mL (95% CI 3·42–11·23)

McKnight RF et al. Lancet 2012;379:721–728

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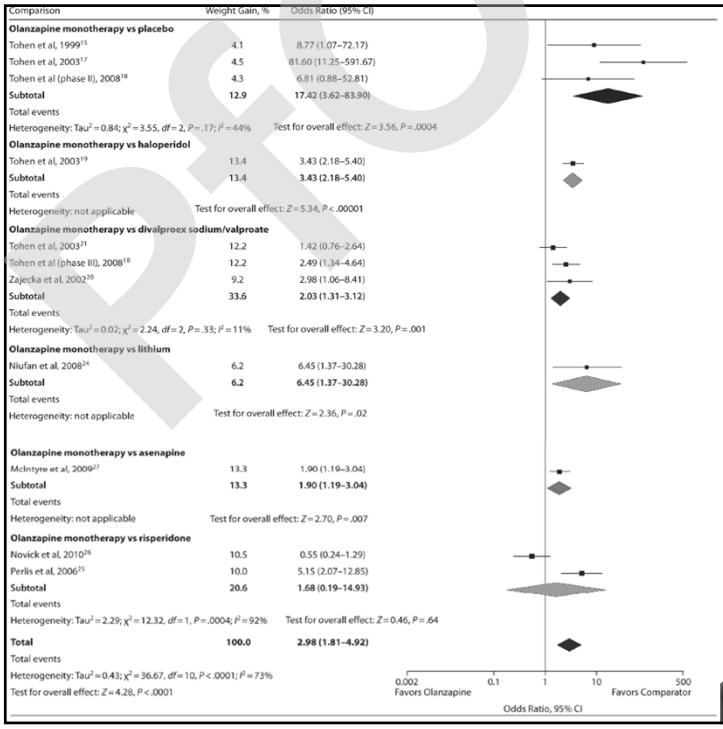
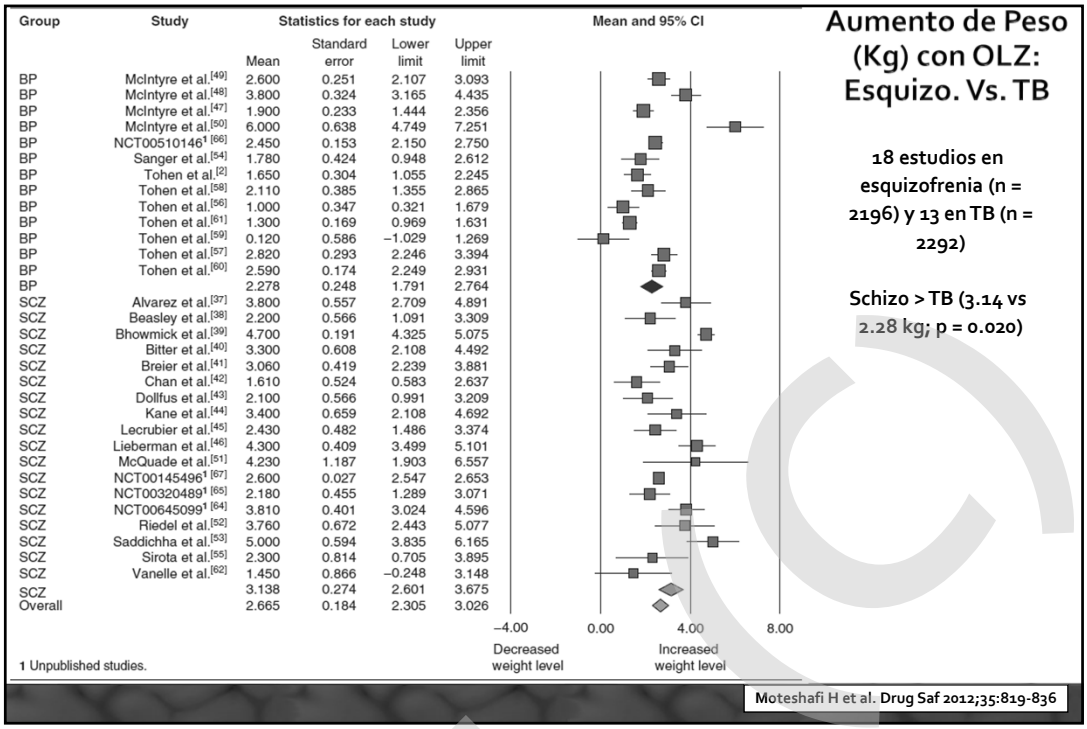


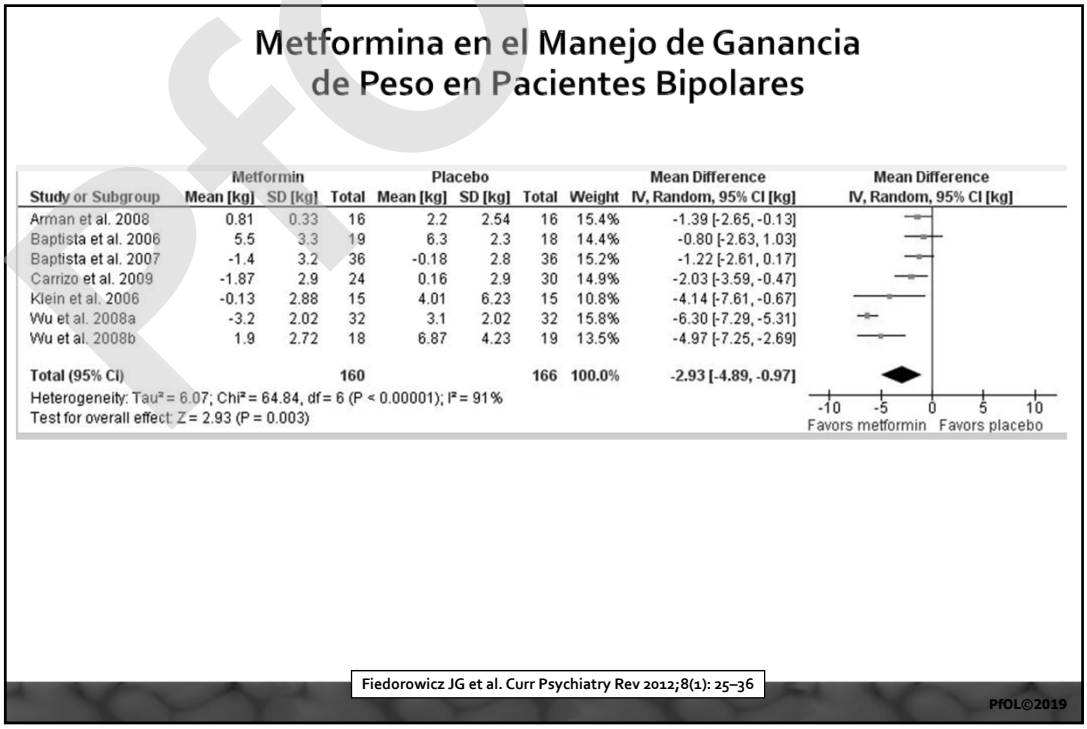
Aumento de Peso (Kg) con OLZ Vs. Otros Eutimizantes

OLZ vs. PLA (2.10 kg; 95%CI, 1.16–3.05)

OLZ vs otro eutimizante (1.34 kg; 95%CI, 0.95–1.72)

Nashed MG et al. Prim Care Companion CNS Disord 2011;13(6)





Topiramato en el Manejo de Ganancia de Peso en Pacientes Bipolares

Study or Subgroup	Topiramate Mean [kg]	Topiramate SD [kg]	Topiramate Total	Placebo Mean [kg]	Placebo SD [kg]	Placebo Total	Weight	Mean Difference IV, Random, 95% CI [kg]
Afshar et al. 2009	-2.4	3.93	16	0.49	2.37	16	19.2%	-2.89 [-5.14, -0.64]
Ko et al. 2005 high	-5.35	4.35	17	-0.3	2.59	20	18.9%	-5.05 [-7.41, -2.69]
Ko et al. 2005 low	-1.68	5.3	16	-0.3	2.59	20	17.2%	-1.38 [-4.21, 1.45]
Narula et al. 2010	-1.27	2.28	33	6.03	3.99	34	21.6%	-7.30 [-8.85, -5.75]
Roy Chengappa et al. 2006	-2.5	3.4	86	0.2	3	91	23.2%	-2.70 [-3.65, -1.75]
Total (95% CI)			**168**			**181**	**100.0%**	**-3.95 [-6.12, -1.77]**

Heterogeneity: Tau² = 5.08; Chi² = 29.27, df = 4 (P < 0.00001); I² = 86%
Test for overall effect: Z = 3.55 (P = 0.0004)

Mean Difference IV, Random, 95% CI [kg]
-10 -5 0 5 10
Favors topiramate Favors placebo

Study or Subgroup	Topiramate Mean [kg]	Topiramate SD [kg]	Topiramate Total	Placebo Mean [kg]	Placebo SD [kg]	Placebo Total	Weight	Mean Difference IV, Random, 95% CI [kg]
Afshar et al. 2009	-2.4	3.93	16	0.49	2.37	16	19.4%	-2.89 [-5.14, -0.64]
Ko et al. 2005 high	-5.35	4.35	17	-0.3	2.59	20	18.1%	-5.05 [-7.41, -2.69]
Ko et al. 2005 low	-1.68	5.3	16	-0.3	2.59	20	13.6%	-1.38 [-4.21, 1.45]
Narula et al. 2010	-1.27	2.28	33	6.03	3.99	34	0.0%	-7.30 [-8.85, -5.75]
Roy Chengappa et al. 2006	-2.5	3.4	86	0.2	3	91	48.9%	-2.70 [-3.65, -1.75]
Total (95% CI)			**135**			**147**	**100.0%**	**-2.98 [-4.14, -1.83]**

Heterogeneity: Tau² = 0.48; Chi² = 4.47, df = 3 (P = 0.22); I² = 33%
Test for overall effect: Z = 5.05 (P < 0.00001)

Mean Difference IV, Random, 95% CI [kg]
-10 -5 0 5 10
Favors topiramate Favors placebo

Fiedorowicz JG et al. Curr Psychiatry Rev 2012;8(1): 25–36

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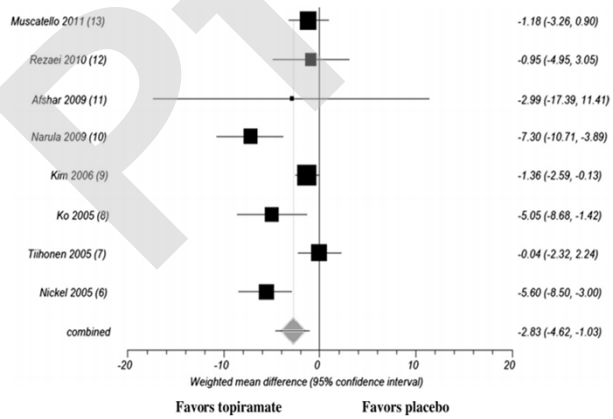
Topiramato en el Manejo de Ganancia de Peso en Pacientes Tratados con Antipsicóticos



Subgroup or Sensitivity Analyses	Body Weight, kg WMD	95% CI
All trials[7–13]	−2.83	−4.62 to −1.03
Adults only[7–11,13]	−3.07	−5.05 to −1.09
Prevention trials[9,10,12]	−3.10	−6.86 to 0.66
Attenuation trials[6–8,11,13]	−2.75	−5.27 to −0.24
Schizophrenia patients only[7–11,13]	−2.53	−4.51 to −0.55
Olanzapine only[6,9,10,13]	−4.52	−8.41 to −0.63
Jadad score ≥ 3[7,8,10–13]	−3.22	−5.54 to −0.91

Mahmood S et al. J Clin Psychopharmacol. 2013 Feb;33(1):90-4

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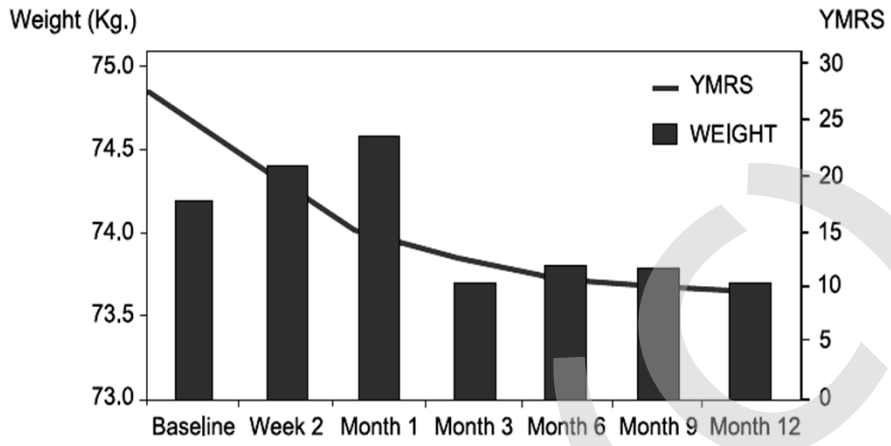
Olanzapina + Topiramato en el Manejo de Ganancia de Peso en Pacientes Bipolares



Vieta E. J Clin Psychopharmacol 2004;24:374–378

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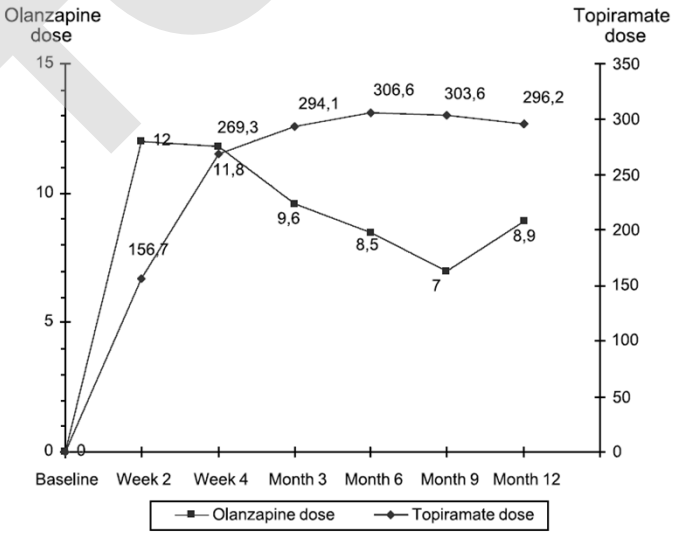
Olanzapina + Topiramato en el Manejo de Ganancia de Peso en Pacientes Bipolares



Vieta E. J Clin Psychopharmacol 2004;24:374–378

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