

# MECANISMOS DE ACCIÓN Y PRESCRIPCIÓN DEL LITIO

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## Declaración de Intereses

- El expositor ha recibido honorarios en calidad de conferencista o como parte de asesorías a las siguientes compañías farmacéuticas:
  - Pfizer
  - GSK
  - Janssen
  - Quideca/Roche
  - MD Pharma/Astra Zeneca
  - Lilly
  - Lundbeck
  - EuroEtika/Bial/Biocodex
  - Sanofi-Aventis
  - Sanfer (Bussié)
- El expositor ha recibido apoyo para participar en actividades de educación médica continuada (CME) por parte de Abbott, Lundbeck, Sanofi-Aventis, Bussié, Pfizer y Lilly

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## Litio en la Historia

- El litio fue descubierto por Arfwedson, un estudiante Sueco de química, en 1817. El nombre de litio proviene del nombre en Griego de una piedra donde fue localizado: "lithos".<sup>1</sup>
- El litio fue usado por primera vez en el S. XIX para condiciones diversas como el bocio y alteraciones neurológicas y gastrointestinales.<sup>2</sup>
- En 1949, John Cade, luego de observar sus propiedades sedantes en animales hace una primera descripción de su efecto antiamaníaco.<sup>3</sup>
- Sólo a partir de 1954, con los trabajos de Mogens Schou, el Litio comienza a ser utilizado ampliamente en Europa y a partir de los sesentas en EUA.<sup>2</sup>

1. Marmol F. Prog Neuropsychopharmacol Biol Psychiatry 2008;32(8):1761-71; 2. Schou M et al. J Neurol Neurosurg Psychiatry 1954;17(4):250-60; 3. Cade JF. Med J Aust 1949;36:349-352;

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*J. Neurol. Neurosurg. Psychiatr., 1954, 17, 250.*

### THE TREATMENT OF MANIC PSYCHOSES BY THE ADMINISTRATION OF LITHIUM SALTS

BY  
M. SCHOU, N. JUEL-NIELSEN, E. STRÖMGREN, and H. VOLDBY  
*From Aarhus University Psychiatric Institute, Sindsgadehospitalet, Risskov, Denmark*

The treatment of manic psychoses with lithium salts was introduced by Cade in 1949, following an accidental observation of a sedative-like action of lithium ions when administered to guinea-pigs. Beneficial effects of this treatment in cases of mania have also been reported by Ashburner (1950) and by Noack and Trautner (1951). According to these reports the effects of lithium treatment are striking, and it is rather astonishing

*Typical Cases*—These were the "pure" manias without any atypical symptoms, cases in which there was no doubt as to the diagnosis of manic-depressive psychosis at any stage of the disease. Delusions, if present, were in obvious accordance with (and most probably secondary to) the patient's mood. Hallucinations were absent or inconspicuous. Contact was always easily obtained with these patients.



Case 2.—A man, aged 52 (67 kg.), at 23 and at 30 years of age had depressions of short duration. For the last 21 years he has been in a mental hospital with regular attacks of mania but no depressions.

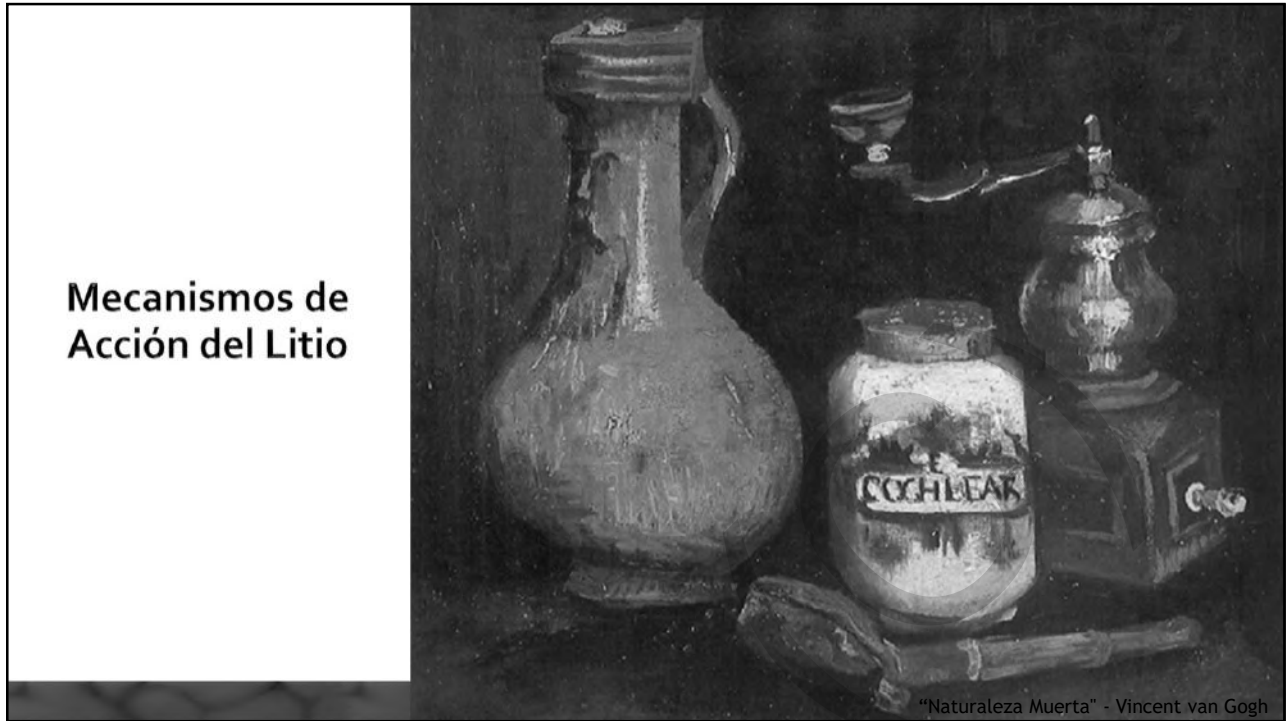
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|------|-------|---------|------------|-------|---------|------------|-------|---------|------------|-------|---------|------------|
| 1951 | manic | neutral | depressive | manic | neutral | depressive | manic | neutral | depressive | manic | neutral | depressive |
| 1952 | manic | neutral | depressive | manic | neutral | depressive | manic | neutral | depressive | manic | neutral | depressive |
| 1953 | manic | neutral | depressive | manic | neutral | depressive | manic | neutral | depressive | manic | neutral | depressive |
| 1954 | manic | neutral | depressive | manic | neutral | depressive | manic | neutral | depressive | manic | neutral | depressive |

64-48-32-16 meq. per day (lithium and/or carbonate)

Schou M et al. J Neurol Neurosurg Psychiatry 1954;17(4):250-60; Cawte J. Aust N Z J Psychiatry 1999; 33: suppl 57-S23

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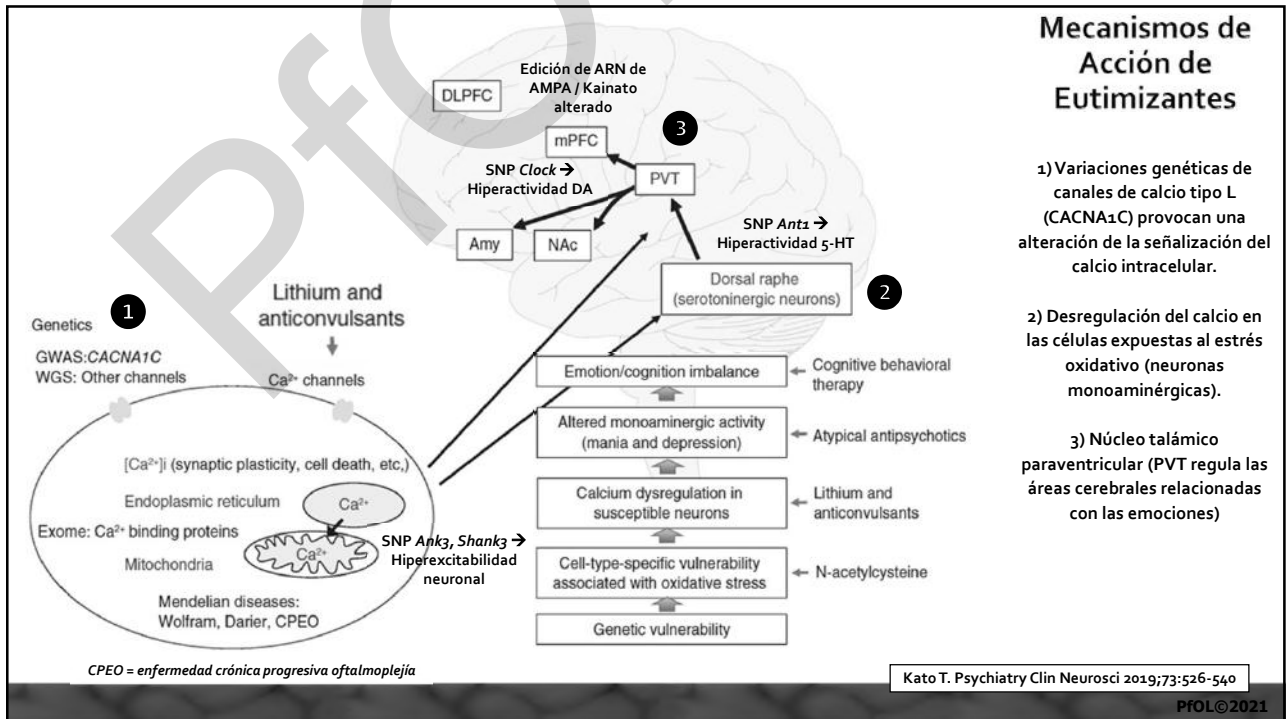
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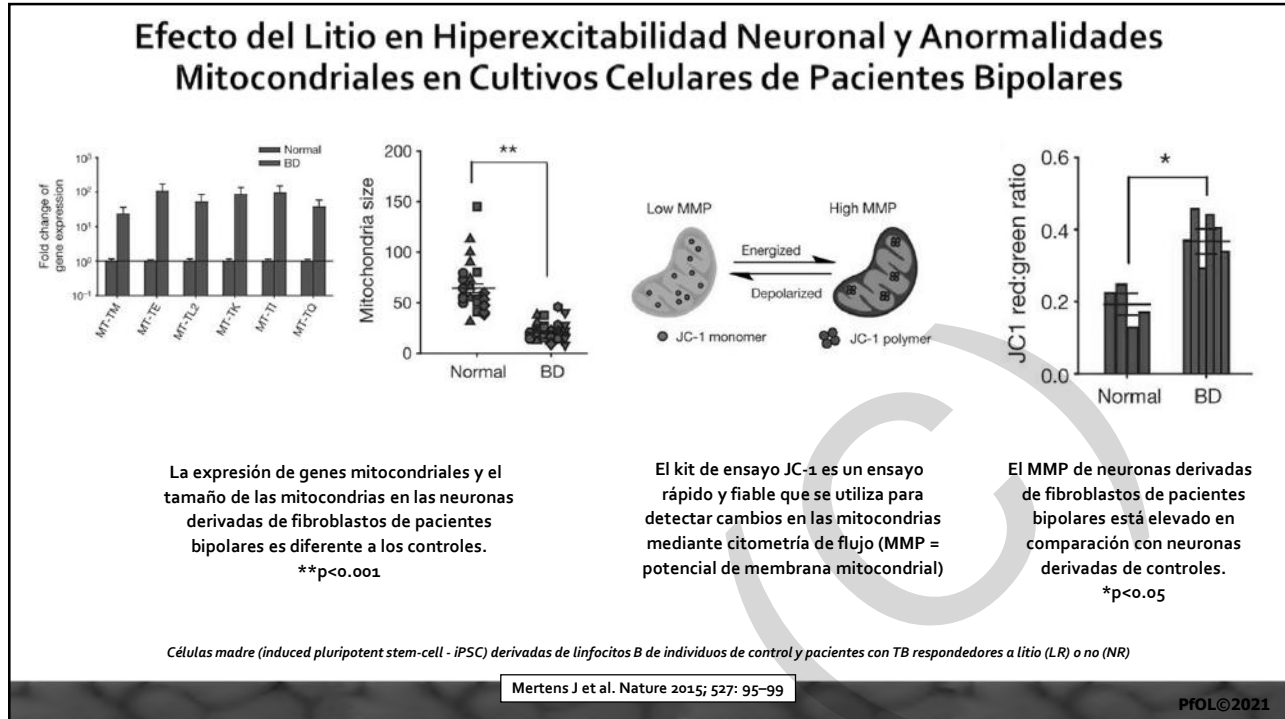
## Mecanismos de Acción del Litio

"Naturaleza Muerta" - Vincent van Gogh

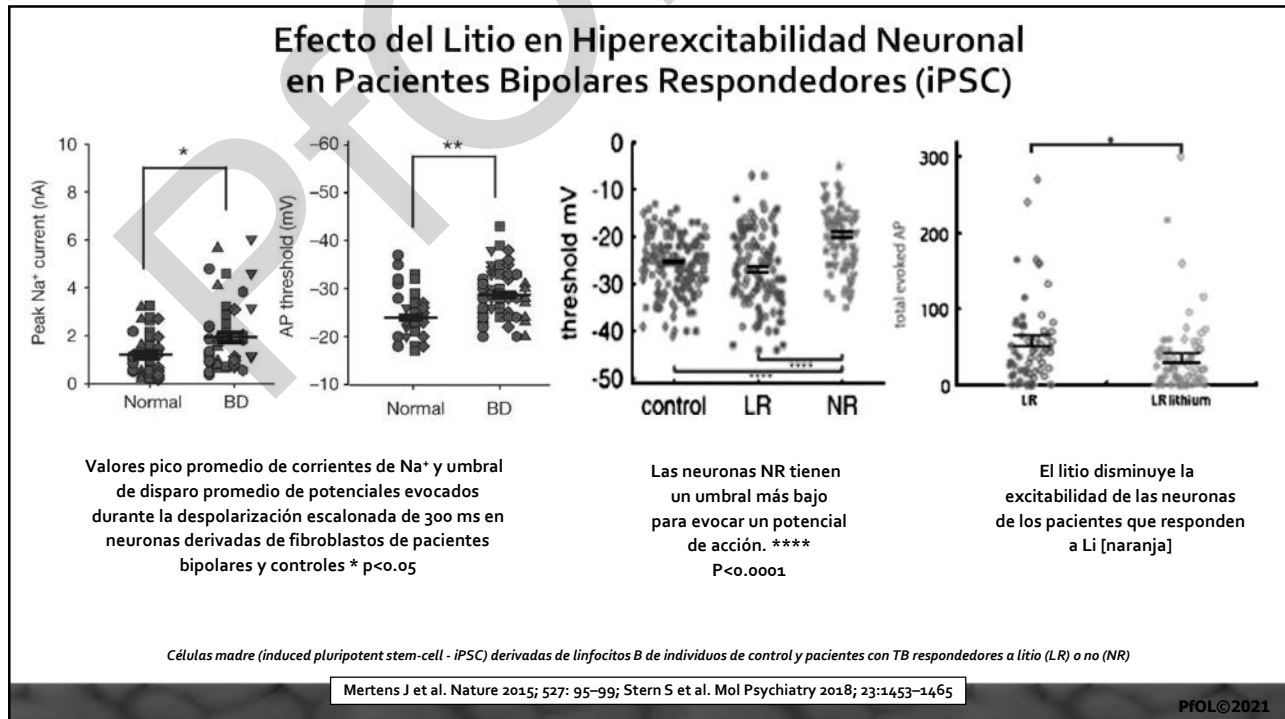
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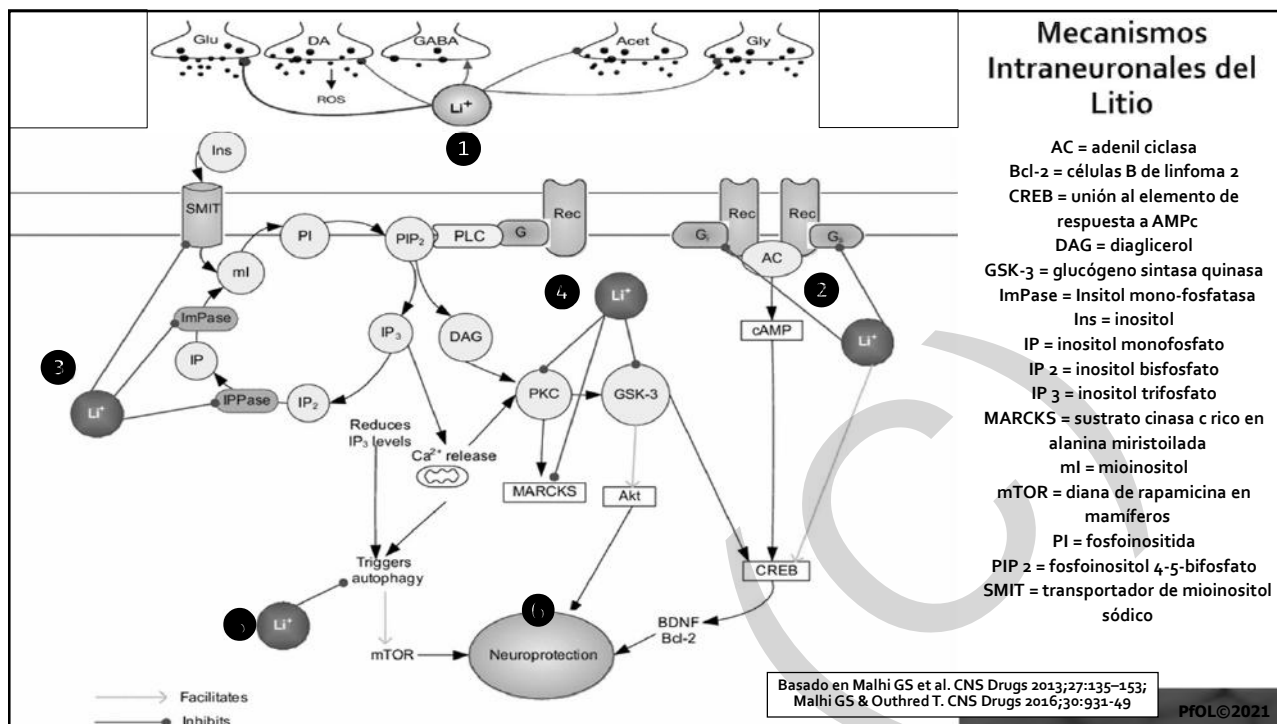
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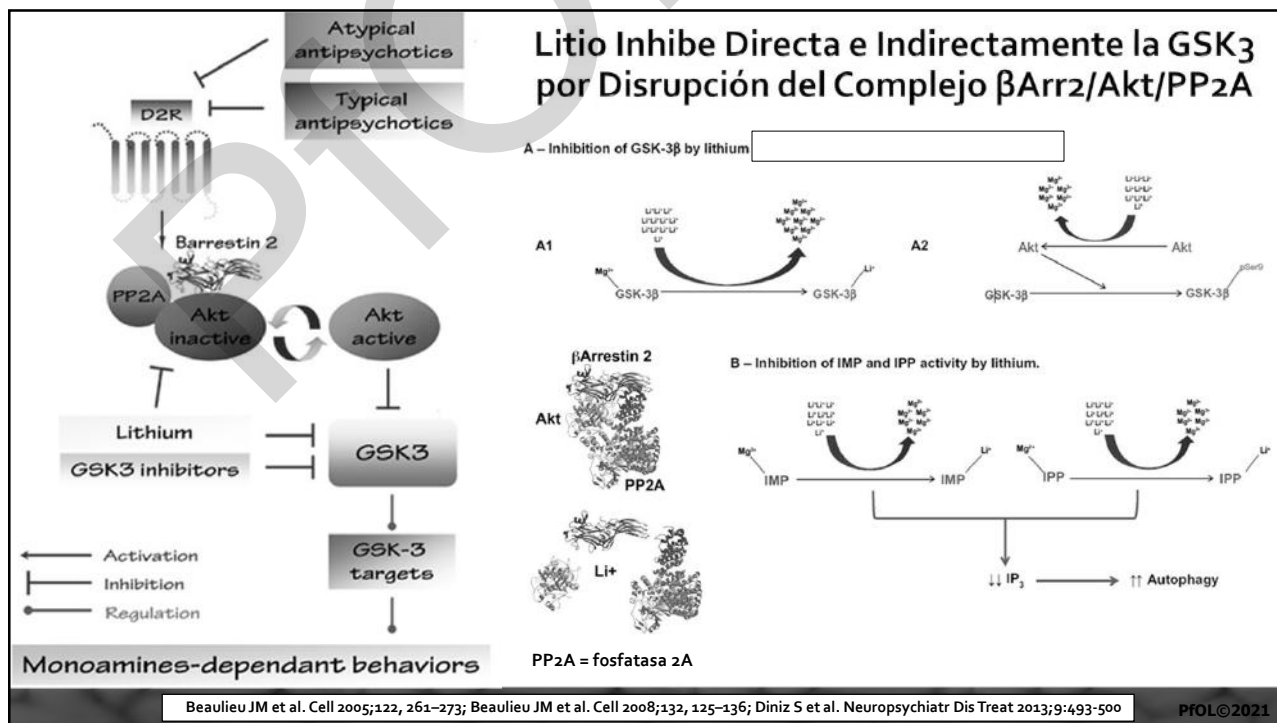
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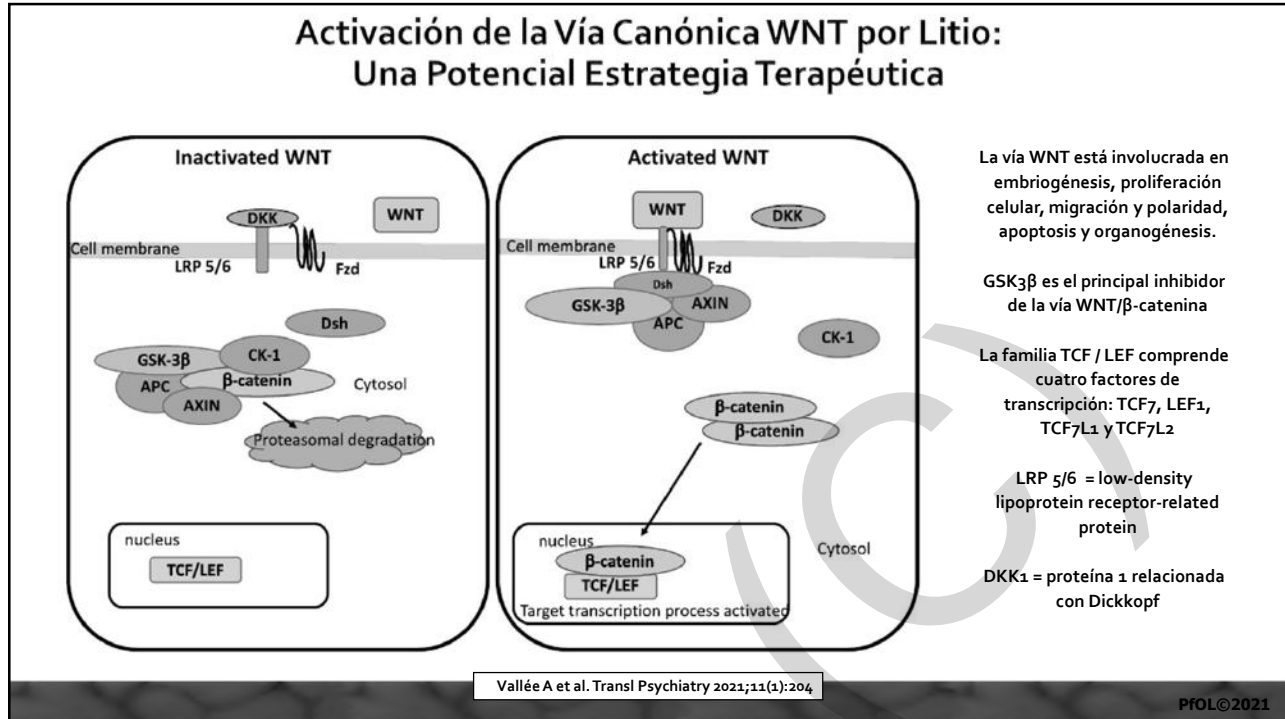
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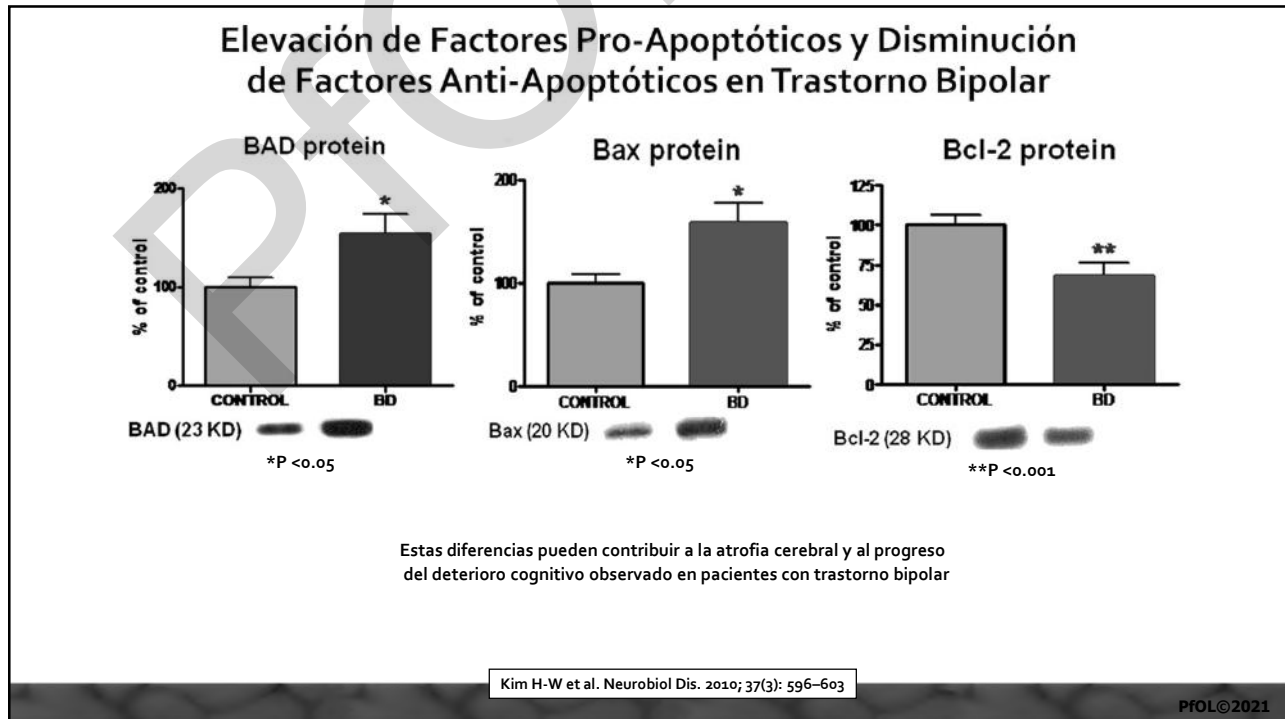
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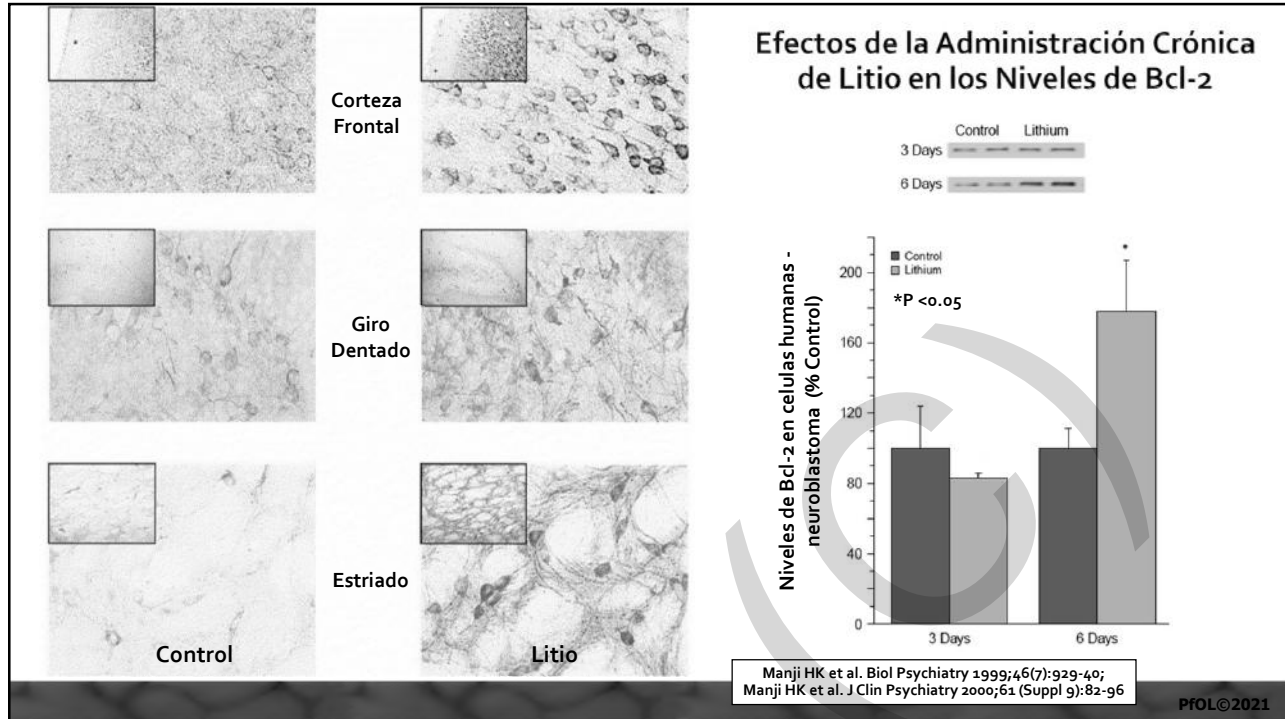
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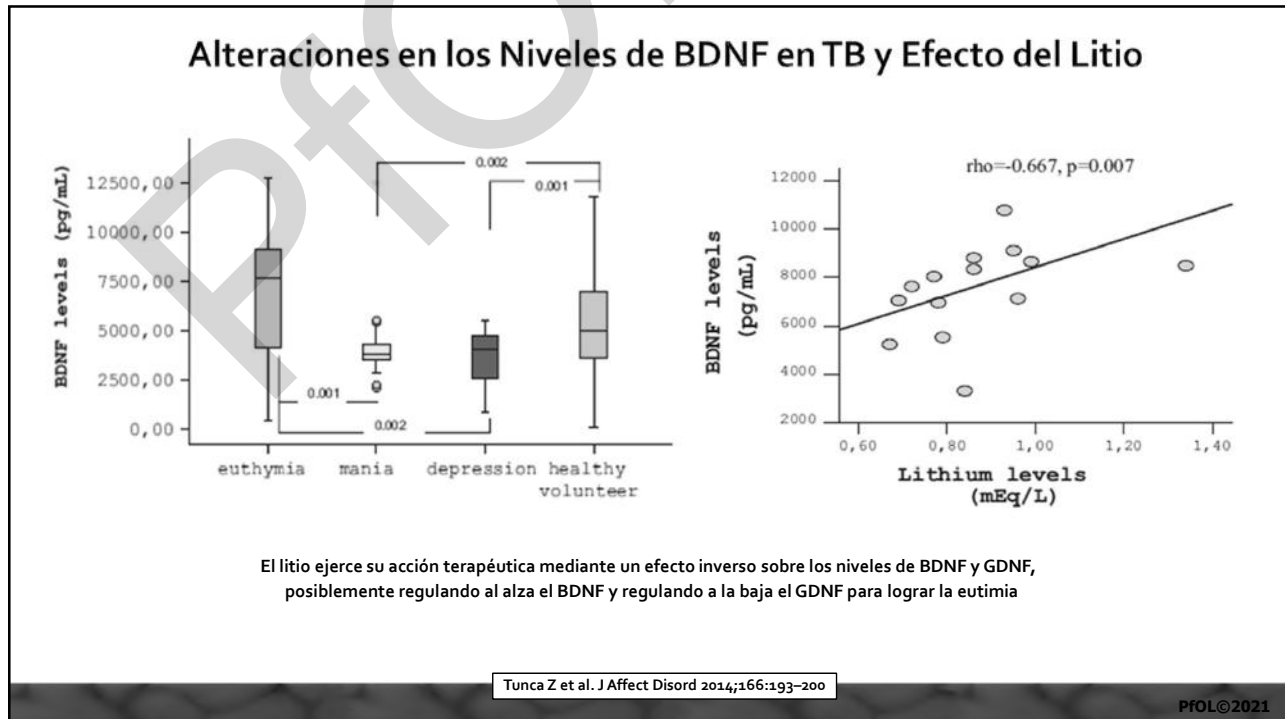
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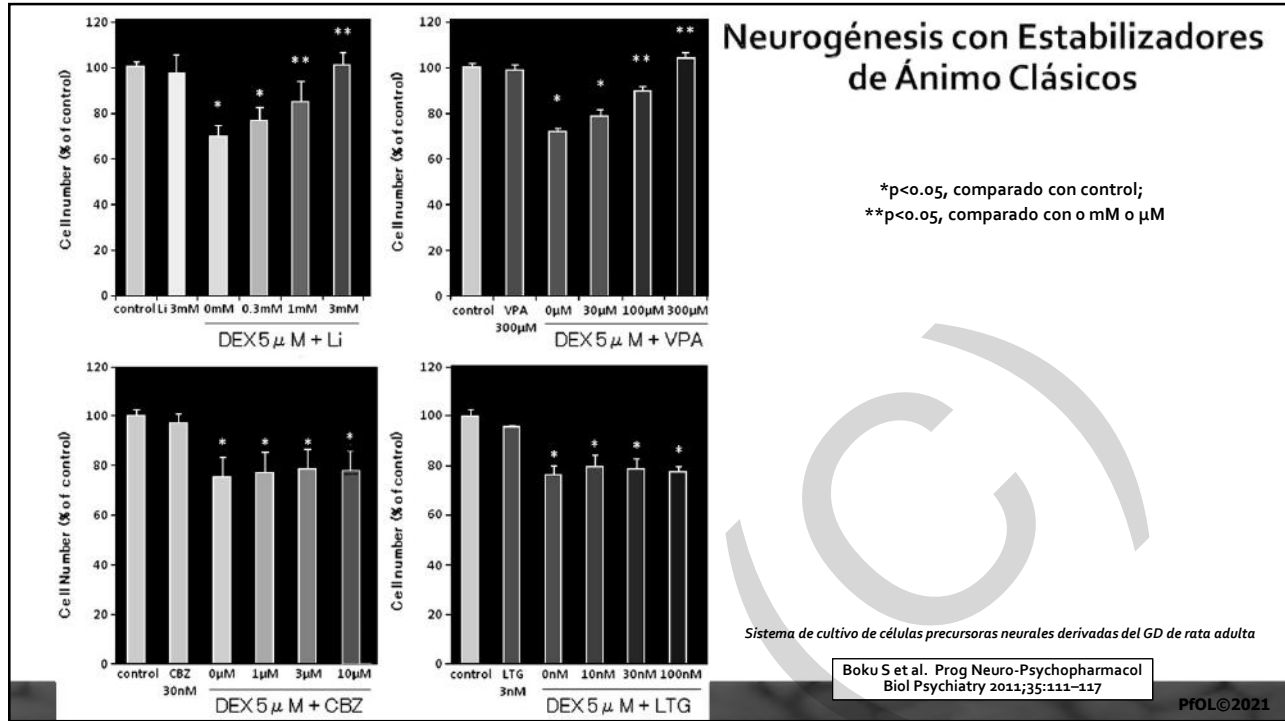
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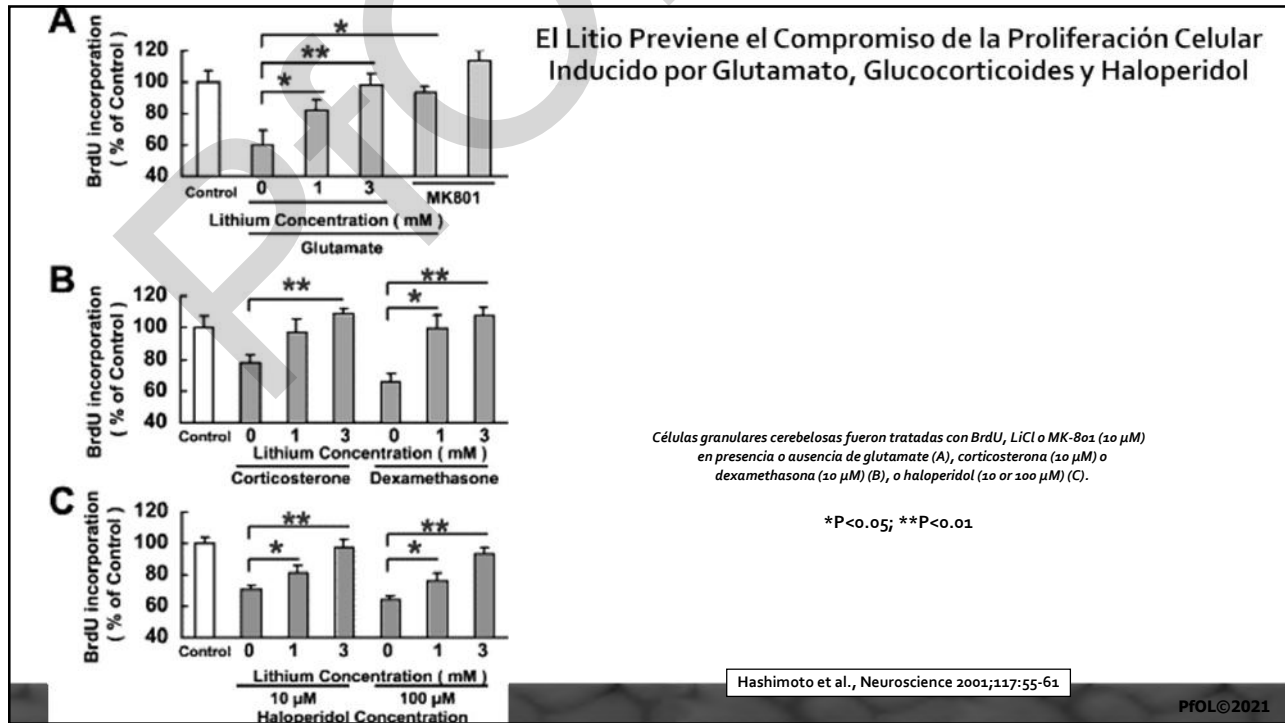
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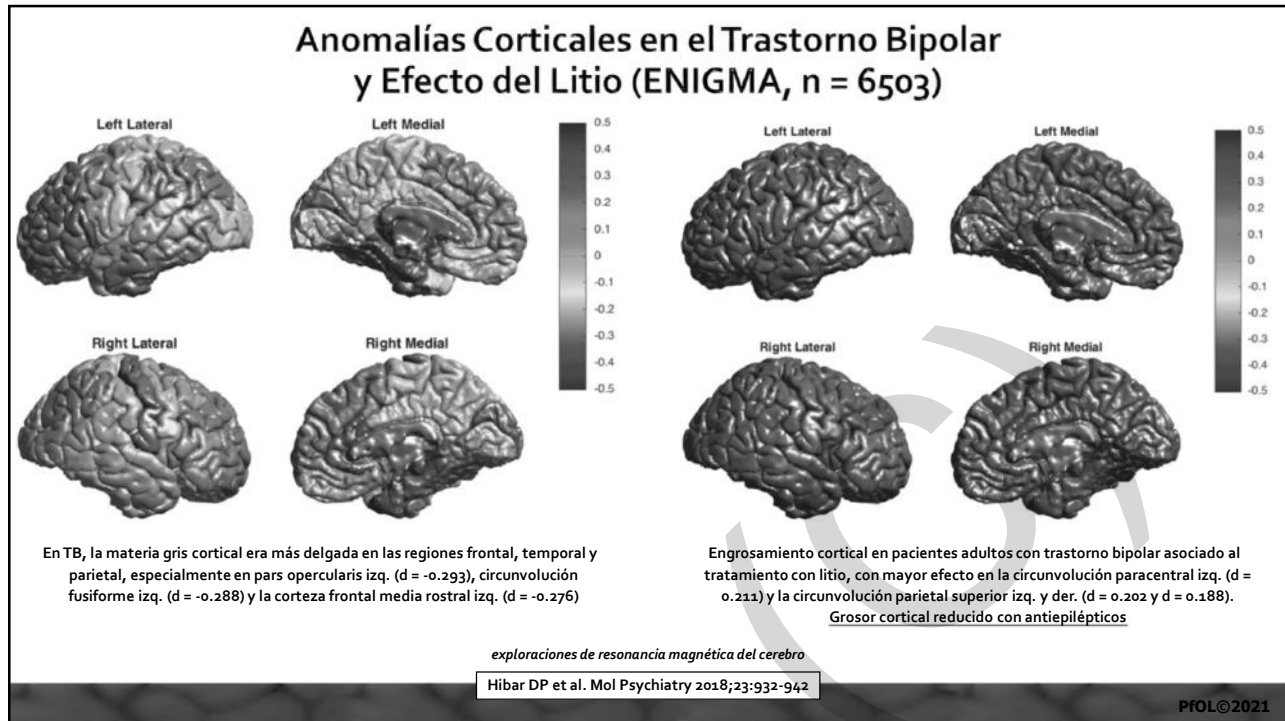
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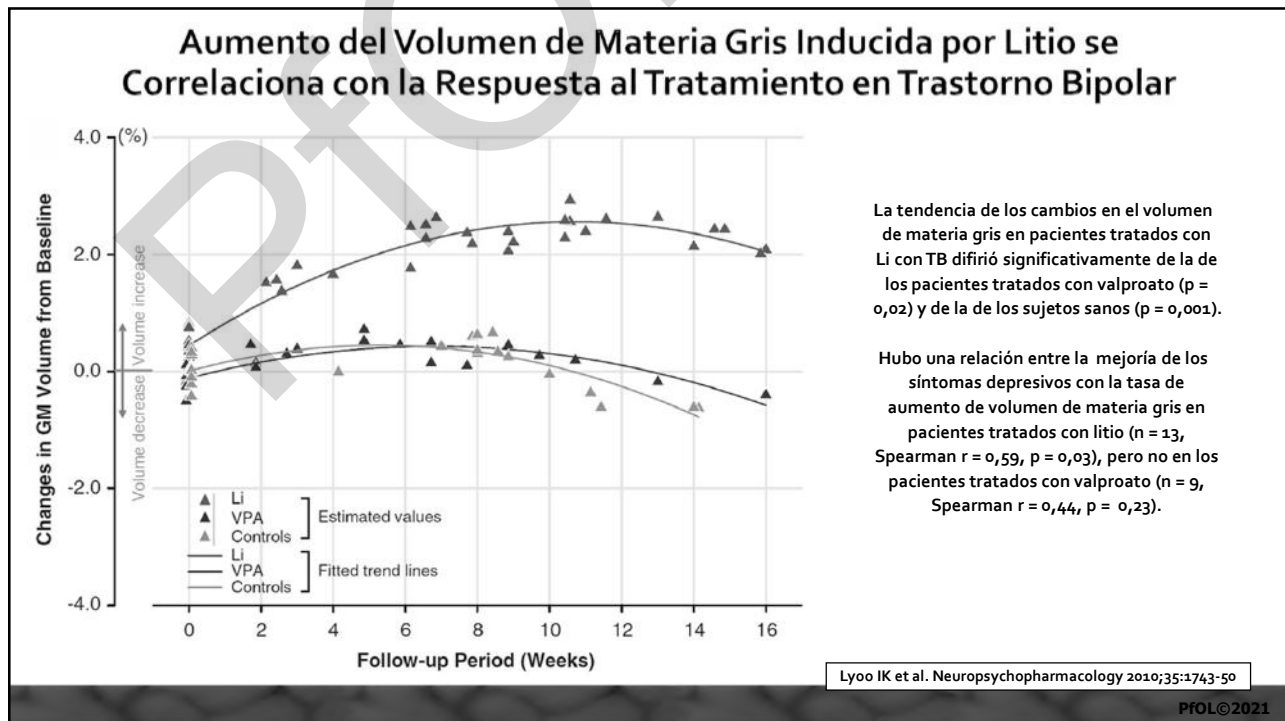
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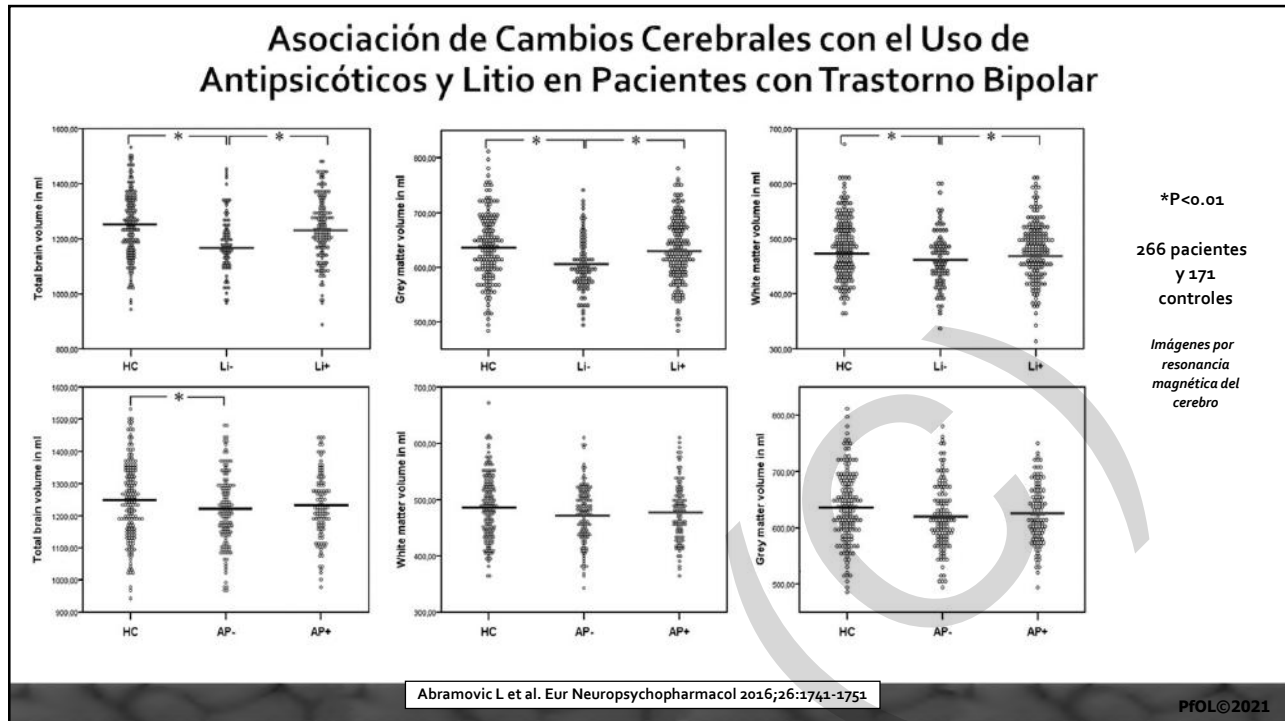
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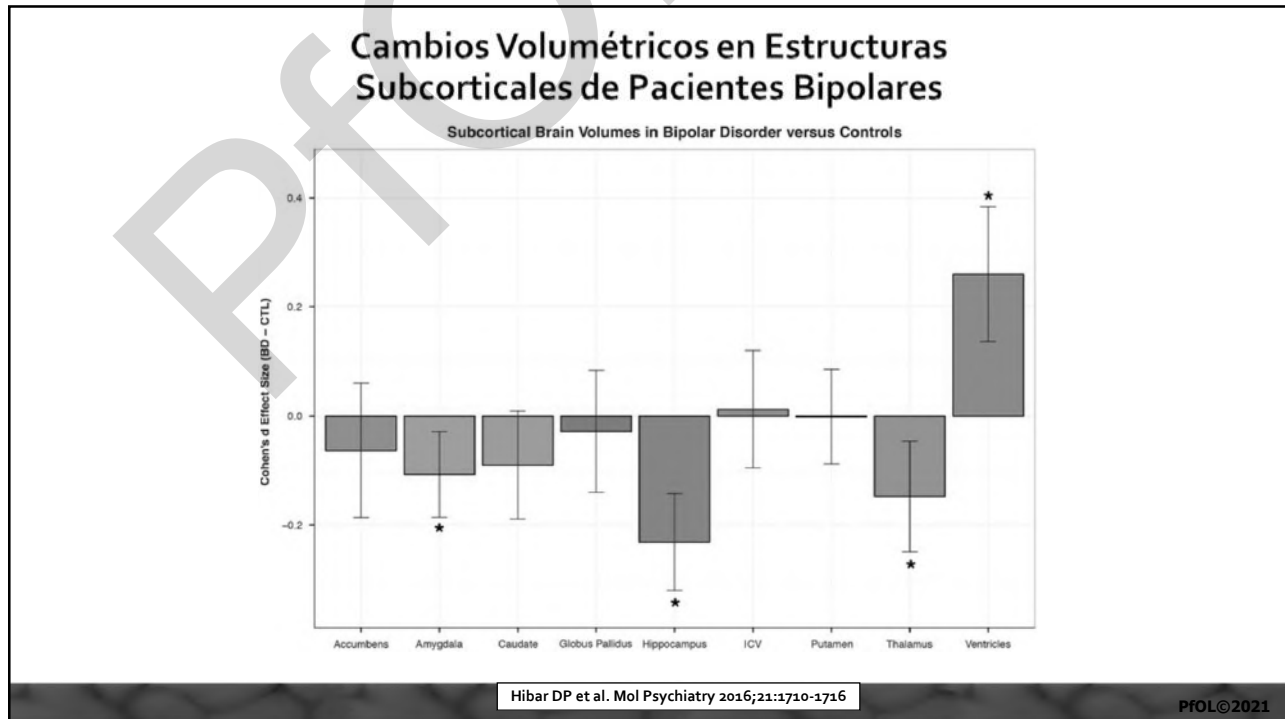
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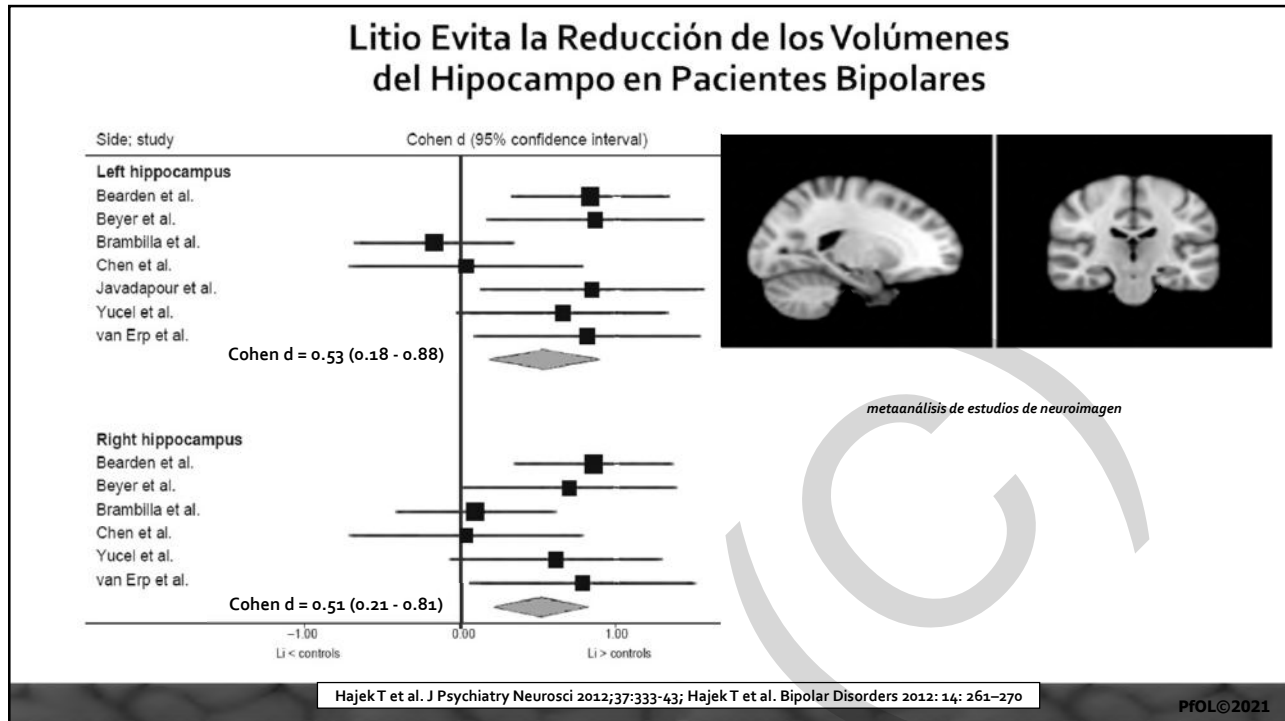
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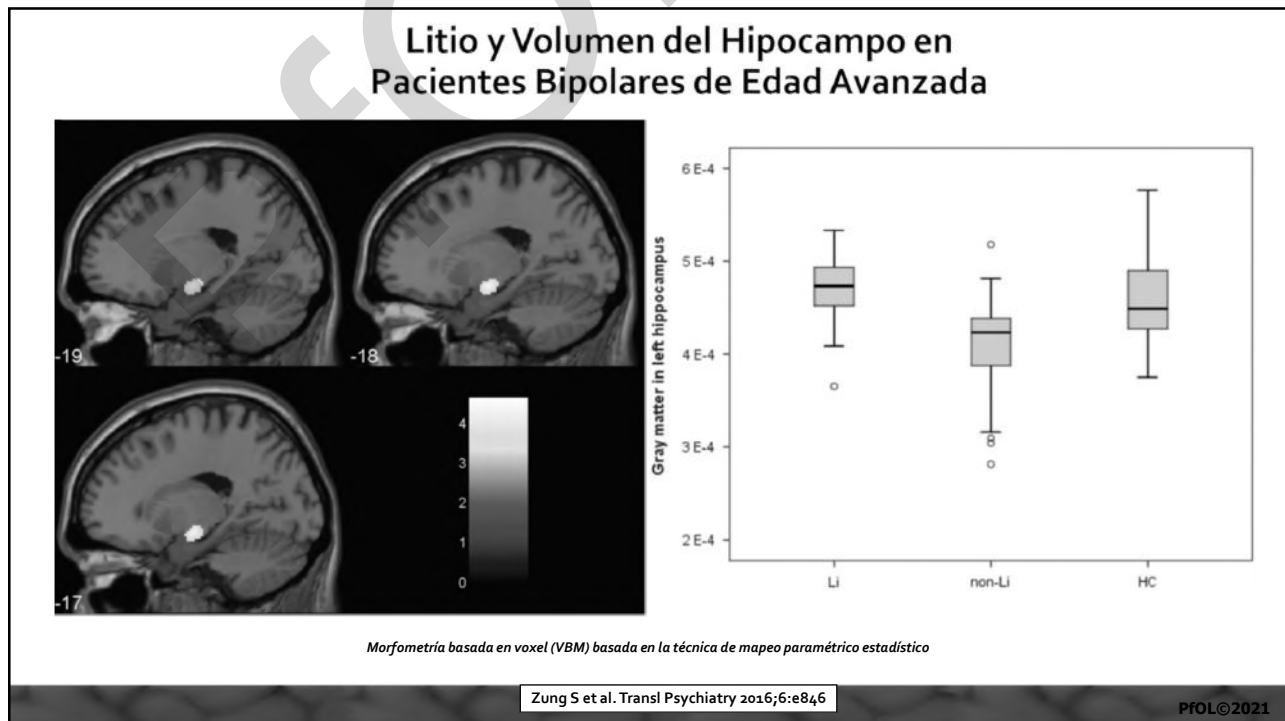
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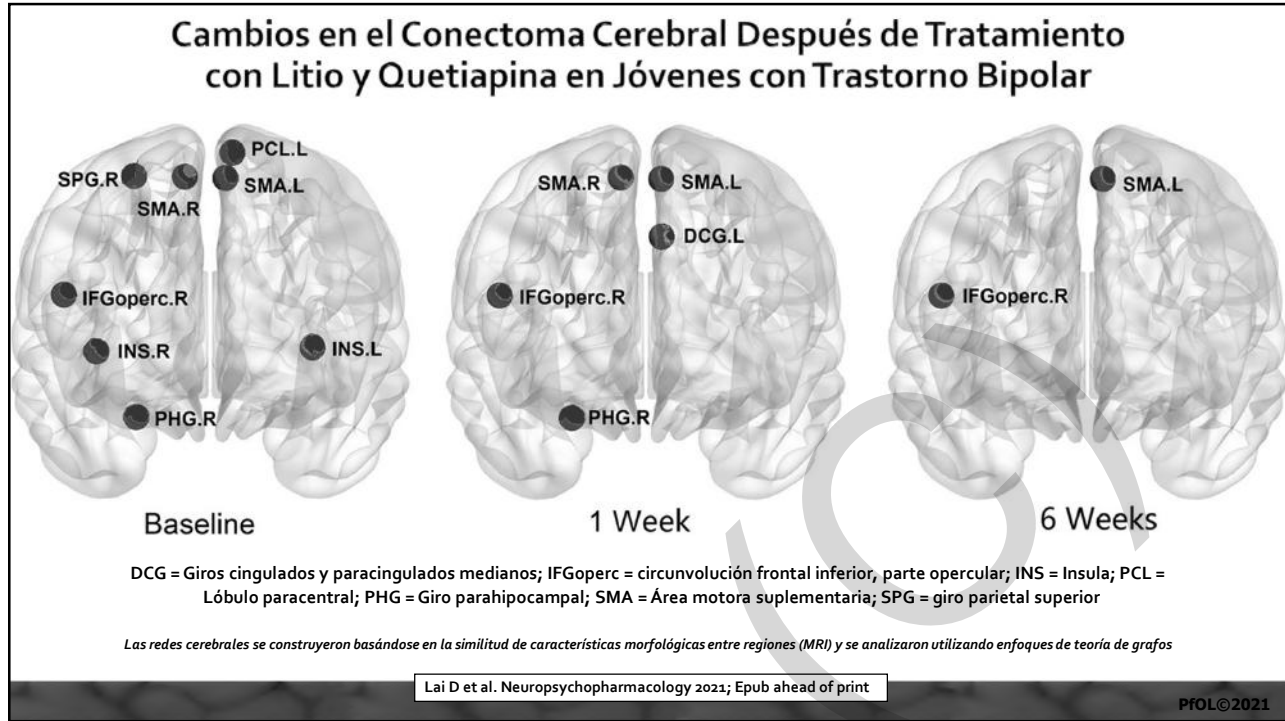
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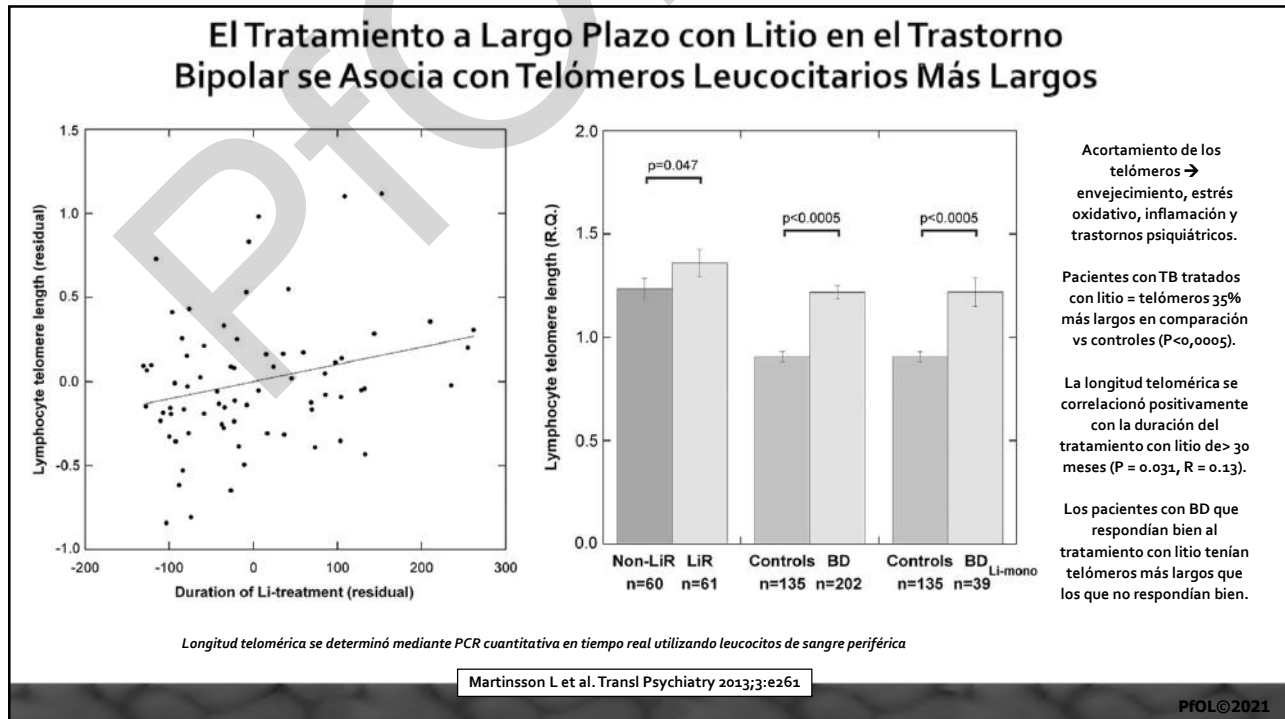
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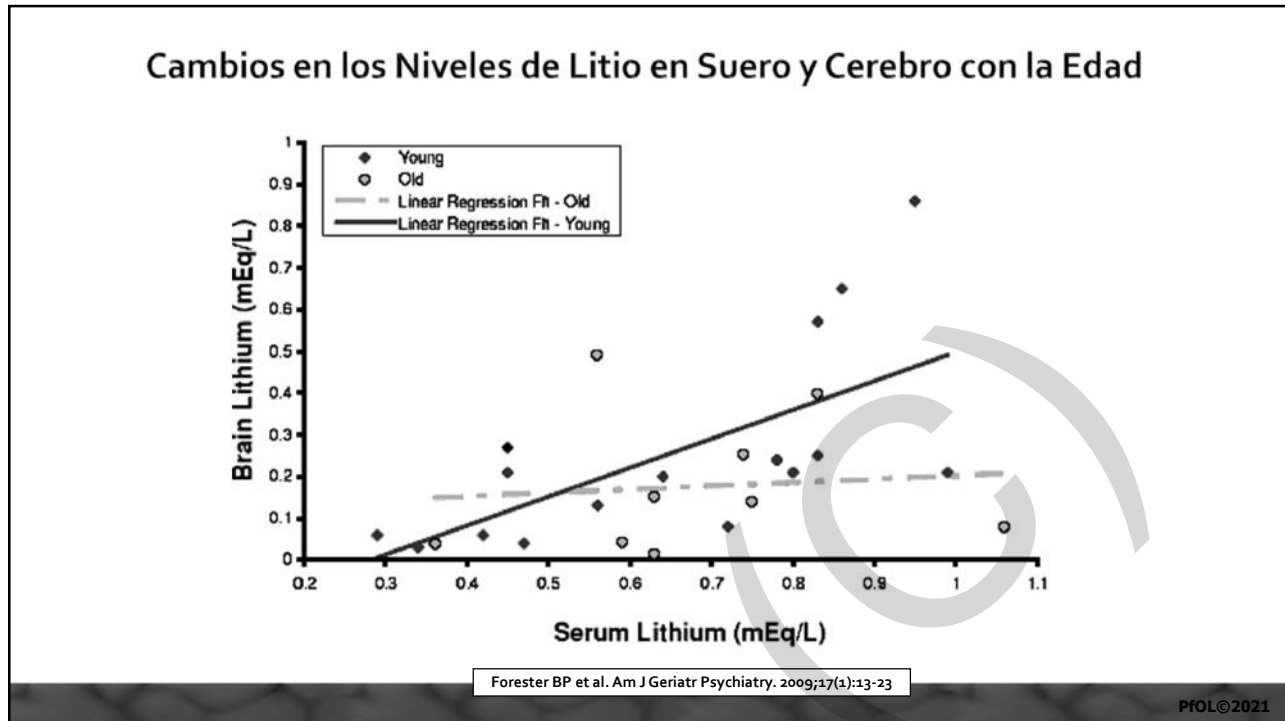
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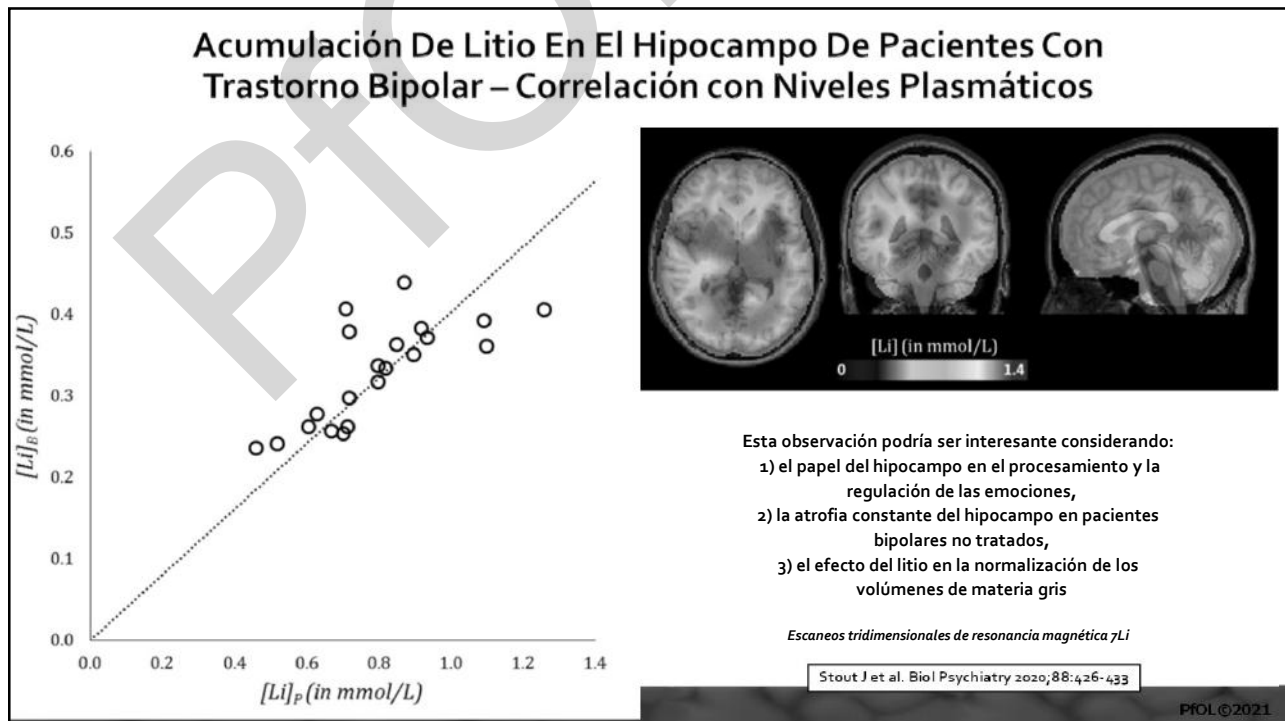
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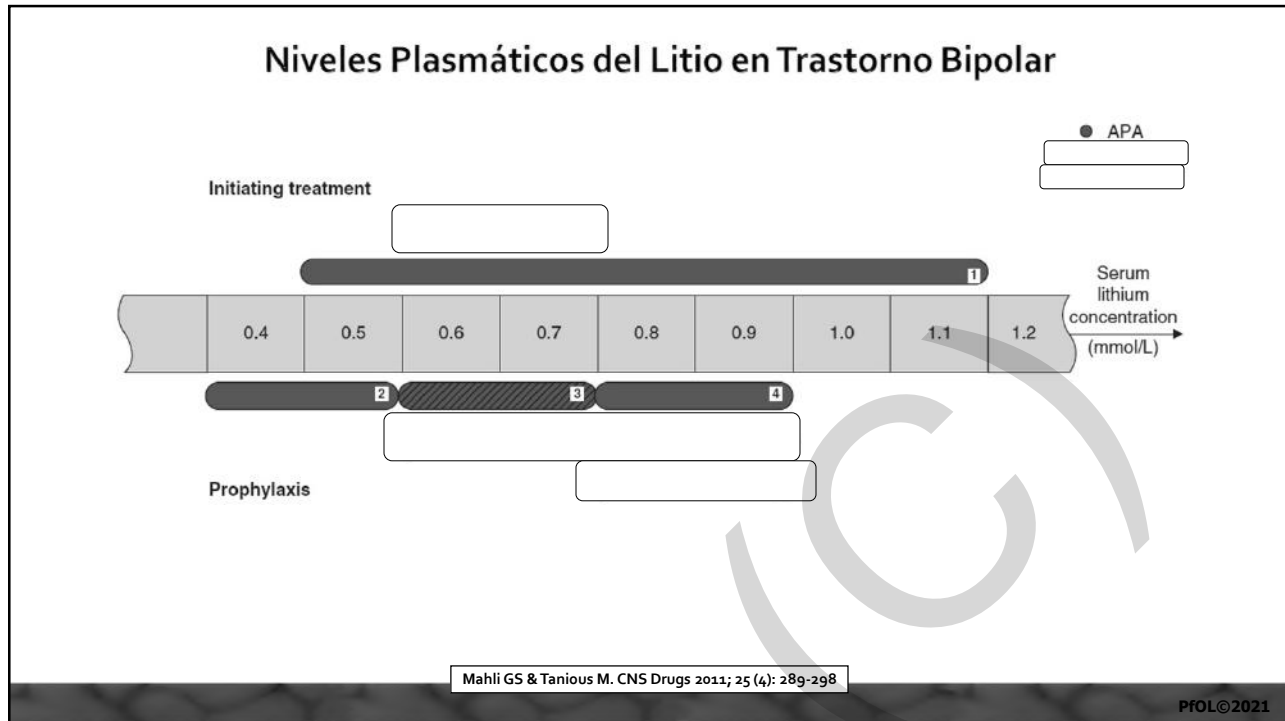
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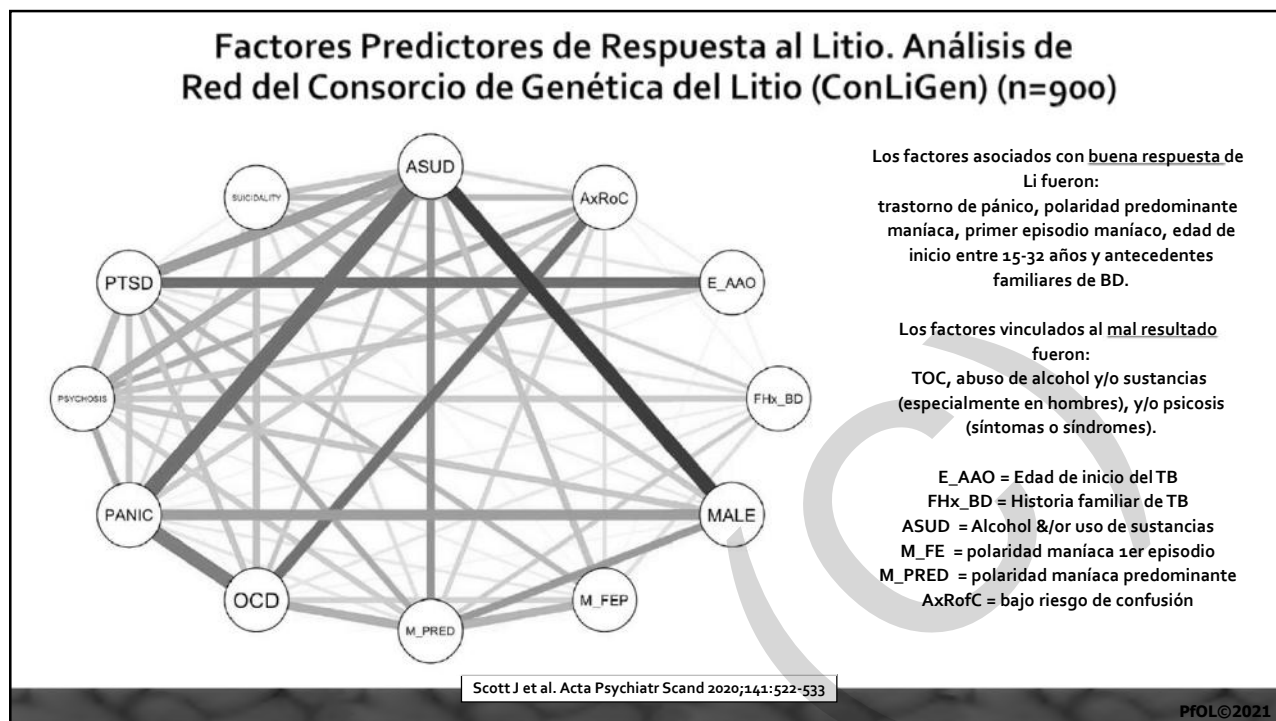
### Evidencia y Guías de Tratamiento Farmacológico en Manía Aguda y Depresión Bipolar

“Jarrón con Doce Girasoles” - Vincent van Gogh

“Hombre con su Cabeza entre sus Manos” - Vincent van Gogh

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### Factores Genéticos Asociados a Respuesta al Litio

- Varios estudios de > 60 diferentes genes han intentado identificar los factores genéticos asociados con respuesta al litio.
- El consorcio ConLiGen con 2563 sujetos genotipados evaluados para la respuesta al litio (GWAS) encontró una asociación significativa de respuesta al tratamiento con un locus en el cromosoma 21, en una región que codifica para 2 ARN largos no codificantes (ARNln): ENSG00000232193 (AL157359.4) y ENSG00000226204 (AL157359.3). La función biológica de estos ARNln se desconoce en gran medida.
- Sin embargo, es muy poco probable que la genética por sí sola pueda producir modelos predictivos significativos. Los estudios deberían caracterizar multidimensionalmente a los pacientes incluyendo genómica, biomarcadores periféricos, neuroimagen multimodal y resultados clínicos.

Papiol S et al. Pharmacopsychiatry 2018;51:206-211

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## Respuesta y Abandonos con 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] <sup>a</sup> |
| Haloperidol   | 9      | 1663     | 9.45 ± 5.65        | 2.47 [1.89–3.25]       | 0.74 [0.53–1.04] <sup>a</sup> |
| Cariprazine   | 4      | 1198     | 7.12 ± 1.89        | 2.33 [1.56–3.53]       | 1.04 [0.63–1.73] <sup>a</sup> |
| 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] <sup>a</sup> |
| Paliperidone  | 5      | 1157     | 7.50 ± 3.87        | 1.72 [1.08–2.74]       | 0.60 [0.33–1.06] <sup>a</sup> |
| Asenapine     | 4      | 841      | 18.3 ± 0.14        | 1.61 [1.03–2.54]       | 0.88 [0.51–1.53] <sup>a</sup> |
| Ziprasidone   | 4      | 839      | 124 ± 7.21         | 1.47 [1.06–2.04]       | 0.93 [0.61–1.41] <sup>a</sup> |

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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### Eficacia y Descontinuación por Cualquier Causa con Eutimizantes en Manía Aguda. Meta-Análisis de Red (SUCRA)

| Drug          | 0.01 | 0.05 | 0.10 | 0.15 | 0.20 | 0.25 | 0.30 | 0.35 | 0.40 | 0.45 | 0.50 | 0.55 | 0.60 | 0.65 | 0.70 | 0.75 | 0.80 | 0.85 | 0.90 | 0.95 | 1.00 |      |
|---------------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|
| Risperidone   | 0.11 | 0.17 | 0.18 | 0.22 | 0.23 | 0.24 | 0.25 | 0.26 | 0.27 | 0.28 | 0.29 | 0.30 | 0.31 | 0.32 | 0.33 | 0.34 | 0.35 | 0.36 | 0.37 | 0.38 | 0.39 | 0.40 |
| Haloperidol   | 0.11 | 0.17 | 0.18 | 0.22 | 0.23 | 0.24 | 0.25 | 0.26 | 0.27 | 0.28 | 0.29 | 0.30 | 0.31 | 0.32 | 0.33 | 0.34 | 0.35 | 0.36 | 0.37 | 0.38 | 0.39 | 0.40 |
| Olanzapine    | 0.11 | 0.17 | 0.18 | 0.22 | 0.23 | 0.24 | 0.25 | 0.26 | 0.27 | 0.28 | 0.29 | 0.30 | 0.31 | 0.32 | 0.33 | 0.34 | 0.35 | 0.36 | 0.37 | 0.38 | 0.39 | 0.40 |
| Cariprazine   | 0.11 | 0.17 | 0.18 | 0.22 | 0.23 | 0.24 | 0.25 | 0.26 | 0.27 | 0.28 | 0.29 | 0.30 | 0.31 | 0.32 | 0.33 | 0.34 | 0.35 | 0.36 | 0.37 | 0.38 | 0.39 | 0.40 |
| Lithium       | 0.11 | 0.17 | 0.18 | 0.22 | 0.23 | 0.24 | 0.25 | 0.26 | 0.27 | 0.28 | 0.29 | 0.30 | 0.31 | 0.32 | 0.33 | 0.34 | 0.35 | 0.36 | 0.37 | 0.38 | 0.39 | 0.40 |
| Carbamazepine | 0.11 | 0.17 | 0.18 | 0.22 | 0.23 | 0.24 | 0.25 | 0.26 | 0.27 | 0.28 | 0.29 | 0.30 | 0.31 | 0.32 | 0.33 | 0.34 | 0.35 | 0.36 | 0.37 | 0.38 | 0.39 | 0.40 |
| Paliperidone  | 0.11 | 0.17 | 0.18 | 0.22 | 0.23 | 0.24 | 0.25 | 0.26 | 0.27 | 0.28 | 0.29 | 0.30 | 0.31 | 0.32 | 0.33 | 0.34 | 0.35 | 0.36 | 0.37 | 0.38 | 0.39 | 0.40 |
| Aripiprazole  | 0.11 | 0.17 | 0.18 | 0.22 | 0.23 | 0.24 | 0.25 | 0.26 | 0.27 | 0.28 | 0.29 | 0.30 | 0.31 | 0.32 | 0.33 | 0.34 | 0.35 | 0.36 | 0.37 | 0.38 | 0.39 | 0.40 |
| Asenapine     | 0.11 | 0.17 | 0.18 | 0.22 | 0.23 | 0.24 | 0.25 | 0.26 | 0.27 | 0.28 | 0.29 | 0.30 | 0.31 | 0.32 | 0.33 | 0.34 | 0.35 | 0.36 | 0.37 | 0.38 | 0.39 | 0.40 |
| Quetiapine    | 0.11 | 0.17 | 0.18 | 0.22 | 0.23 | 0.24 | 0.25 | 0.26 | 0.27 | 0.28 | 0.29 | 0.30 | 0.31 | 0.32 | 0.33 | 0.34 | 0.35 | 0.36 | 0.37 | 0.38 | 0.39 | 0.40 |
| Olanzapine    | 0.11 | 0.17 | 0.18 | 0.22 | 0.23 | 0.24 | 0.25 | 0.26 | 0.27 | 0.28 | 0.29 | 0.30 | 0.31 | 0.32 | 0.33 | 0.34 | 0.35 | 0.36 | 0.37 | 0.38 | 0.39 | 0.40 |
| Ziprasidone   | 0.11 | 0.17 | 0.18 | 0.22 | 0.23 | 0.24 | 0.25 | 0.26 | 0.27 | 0.28 | 0.29 | 0.30 | 0.31 | 0.32 | 0.33 | 0.34 | 0.35 | 0.36 | 0.37 | 0.38 | 0.39 | 0.40 |
| Valproate     | 0.11 | 0.17 | 0.18 | 0.22 | 0.23 | 0.24 | 0.25 | 0.26 | 0.27 | 0.28 | 0.29 | 0.30 | 0.31 | 0.32 | 0.33 | 0.34 | 0.35 | 0.36 | 0.37 | 0.38 | 0.39 | 0.40 |
| Verapamil     | 0.11 | 0.17 | 0.18 | 0.22 | 0.23 | 0.24 | 0.25 | 0.26 | 0.27 | 0.28 | 0.29 | 0.30 | 0.31 | 0.32 | 0.33 | 0.34 | 0.35 | 0.36 | 0.37 | 0.38 | 0.39 | 0.40 |
| Lamotrigine   | 0.11 | 0.17 | 0.18 | 0.22 | 0.23 | 0.24 | 0.25 | 0.26 | 0.27 | 0.28 | 0.29 | 0.30 | 0.31 | 0.32 | 0.33 | 0.34 | 0.35 | 0.36 | 0.37 | 0.38 | 0.39 | 0.40 |
| Licarbazepine | 0.11 | 0.17 | 0.18 | 0.22 | 0.23 | 0.24 | 0.25 | 0.26 | 0.27 | 0.28 | 0.29 | 0.30 | 0.31 | 0.32 | 0.33 | 0.34 | 0.35 | 0.36 | 0.37 | 0.38 | 0.39 | 0.40 |
| Placebo       | 0.11 | 0.17 | 0.18 | 0.22 | 0.23 | 0.24 | 0.25 | 0.26 | 0.27 | 0.28 | 0.29 | 0.30 | 0.31 | 0.32 | 0.33 | 0.34 | 0.35 | 0.36 | 0.37 | 0.38 | 0.39 | 0.40 |

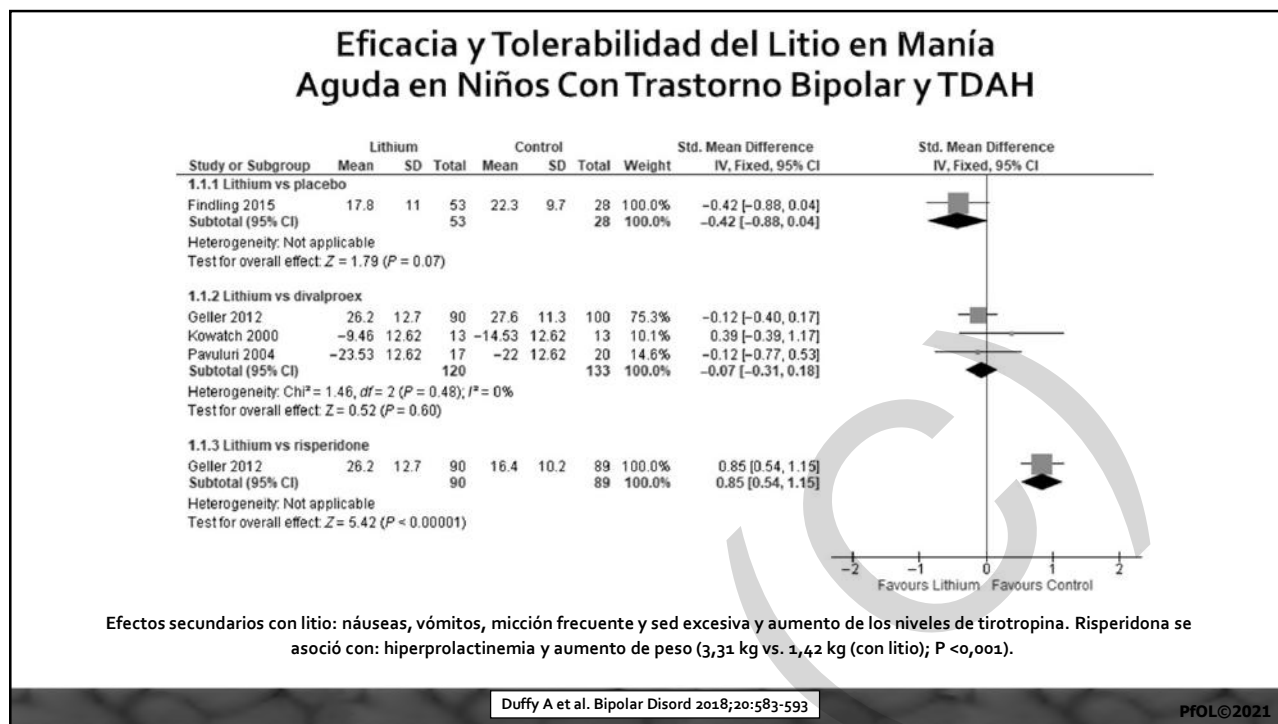
Crema = eficacia (SMD, g de Hedges)

Azul = interrupción por cualquier causa (OR)

Yildiz A et al. Psychol Med 2015;45:299-317

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### Combinación Litio + Antipsicótico en Episodios Maníacos

| Variable                | Terapia Combinada |       | Diferencia Media - 95% CI |
|-------------------------|-------------------|-------|---------------------------|
|                         | NO                | SI    |                           |
| Total N                 | 940               | 495   | -                         |
| Días de hospitalización | 14.3              | 11.5  | 2.83; 1.13 a 4.53         |
| Costos en US\$          | 38555             | 41560 | -3004; -11629 a 5261      |

Al usar litio en manía aguda, comenzar el régimen combinado desde el día inicial de la hospitalización debe considerarse como un modelo eficaz para una respuesta más rápida sin costos adicionales.

Lee HK et al. Cureus 2020;12(6): e8568 PFOL©2021

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

| Treatments (trials)      | Subjects (n) | Dropout (%) Drug/Placebo | Responders/Subjects |                  | RR [95%CI]        |
|--------------------------|--------------|--------------------------|---------------------|------------------|-------------------|
|                          |              |                          | Drug (%)            | Placebo (%)      |                   |
| <i>Lithium</i>           |              |                          |                     |                  |                   |
| Lithium [Li] (1)         | 265          | 25.0/27.8                | 85/136 (62.5)       | 72/129 (55.8)    | 1.12 [0.92–1.37]* |
| <i>Anticonvulsants</i>   |              |                          |                     |                  |                   |
| 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]  |
| <i>Antipsychotics</i>    |              |                          |                     |                  |                   |
| Aripiprazole [APZ] (2)   | 690          | 44.0/32.4                | 148/337 (43.9)      | 147/353 (41.6)   | 1.10 [0.81–1.48]* |
| 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]* |
| 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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### Tratamiento de los Síntomas Mixtos en Trastorno Bipolar

|                                            | Acute mania/hypomania with mixed features |                     | Acute depression with mixed features |                     |
|--------------------------------------------|-------------------------------------------|---------------------|--------------------------------------|---------------------|
|                                            | Manic symptoms                            | Depressive symptoms | Manic symptoms                       | Depressive symptoms |
| <i>Atypical antipsychotics (AAP)</i>       |                                           |                     |                                      |                     |
| Aripiprazole (monotherapy)                 | +                                         |                     |                                      |                     |
| Asenapine (monotherapy)                    | +                                         | +                   |                                      |                     |
| Cariprazine (monotherapy)                  | +                                         | -                   | -                                    | +                   |
| Lurasidone (monotherapy)                   |                                           |                     | -                                    | +                   |
| Olanzapine (monotherapy)                   | +                                         | -                   | +                                    | +                   |
| Quetiapine (adjunctive/monotherapy)        | +                                         | -                   | +                                    | +                   |
| Quetiapine (adjunctive/monotherapy)        | -                                         | +                   |                                      |                     |
| Risperidone (adjunctive)                   | +                                         | +                   |                                      |                     |
| Ziprasidone (monotherapy/adjunctive)       | +                                         | +                   | +                                    | +                   |
| <i>Mood stabilizers (MS)</i>               |                                           |                     |                                      |                     |
| Lithium                                    | -                                         |                     |                                      |                     |
| DVP                                        | +                                         |                     |                                      |                     |
| <i>Combination AAP/MS + antidepressant</i> |                                           |                     |                                      |                     |
| Olanzapine + fluoxetine                    |                                           |                     | +                                    | +                   |
| AAP/MS + antidepressant (multiple agents)  |                                           |                     |                                      | -                   |

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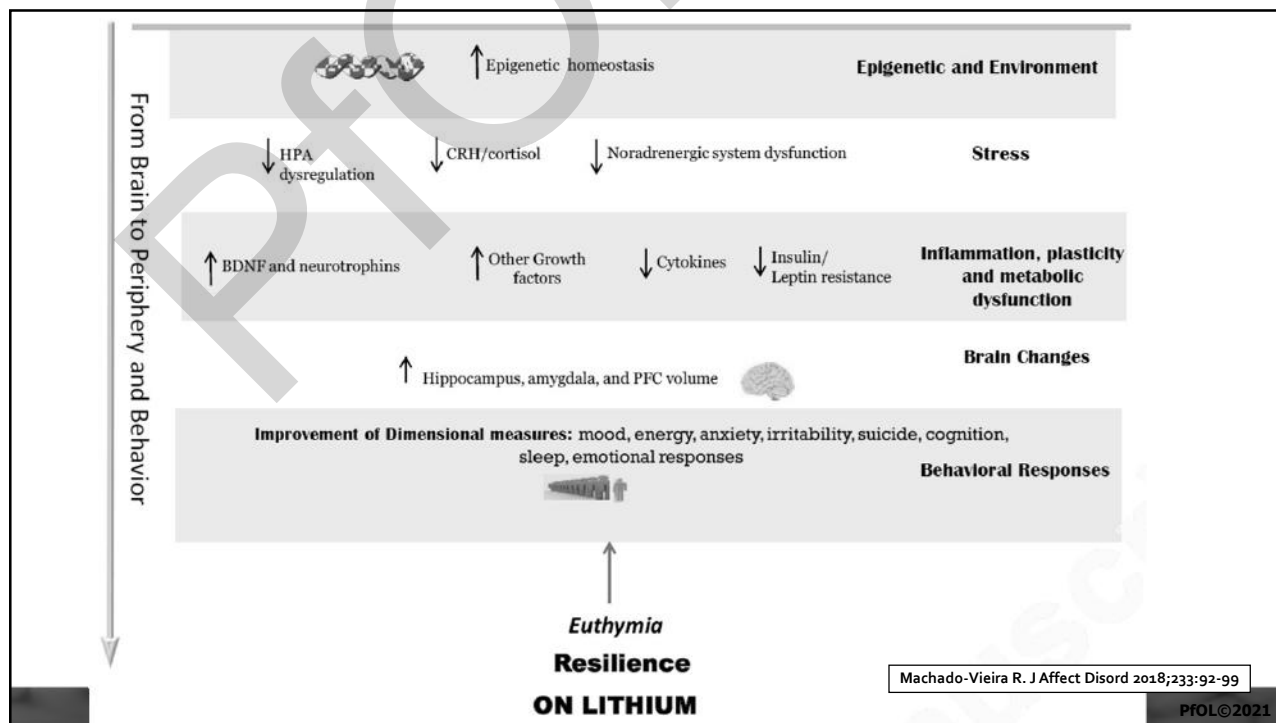
## Eventos Adversos del Litio. Meta-Análisis

- Reducción en la capacidad para concentrar la orina en un 15% (-158-43 mOsm/kg;  $p < 0.0001$ ).
- Leve incremento en el riesgo de falla renal (0.5% de los paciente recibieron terapia de remplazo renal).
- Hipotiroidismo versus placebo (OR = 5.78; 2.00–16.67) y aumento de la TSH (4.00 iU/mL;  $p < 0.0001$ ).
- Aumento del  $Ca^{++}$  sérico (+0.09 mmol/L;  $p = 0.009$ ) y de la hormona paratiroidea (+7.32 pg/mL;  $p < 0.0001$ ).
- Ganancia de peso versus placebo (OR = 1.89; 1.27–2.82), pero menor que con olanzapina.
- Temblor postural (temblor fisiológico exagerado). Responde a  $\beta$ -bloqueadores, BZDs, gabapentina y topiramato.<sup>2</sup>
- Malformaciones cardíacas (OR [MA] = 1.86; 1.16–2.96) [ $< 0.64$  mEq/L sin malformaciones cardíacas]<sup>3</sup> y aborto espontáneo (OR [MA] = 3.77; 1.15–12.39)<sup>4</sup>

McKnight RF. Lancet 2012; 379: 721–28; 2. Baek JH et al. Acta Psychiatr Scand 2014;129:17-23; 3. Fornaro M et al. Am J Psychiatry 2020;177:76-92; 4. Grigoriadis S et al. Can J Psychiatry 2020;65:821-834

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