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Psiquiatria nutricional aplicada al trastorno bipolar

Susana Patrícia Gomes da Costa

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Psiquiatría nutricional aplicada al trastorno bipolar

Memoria de tesis doctoral presentada por:

Susana Patrícia Gomes da Costa

para optar al grado de doctora por la Universidad de Barcelona.

Dirigida por:

Prof. Dr. Eduard Vieta Pascual, Universidad de Barcelona

Dra. Isabella Pacchiarotti, Universidad de Barcelona

Tutor:

Prof. Dr. Eduard Vieta Pascual, Universidad de Barcelona

Programa de Doctorado Medicina e Investigación Traslacional.

Facultad de Medicina y Ciencias de la Salud.

Universidad de Barcelona.

Octubre 2024

Agradecimientos

No es posible reconocer a todas las personas que han contribuido al presente trabajo, ya que cada contribución es única y necesaria. Gracias a todos.

A Eduard, por confiar y creer en mí. Por ser una fuente de inspiración, por su calidez, proximidad y confianza durante los últimos años.

A Isabella, cercana y pragmática cuando es necesario, compañera en el campo de batalla. Gracias por su orientación, consejo y apoyo.

A mi familia, por su amor incondicional y apoyo siempre. A mis padres por el soporte e insistencia en la importancia de seguir adelante, siempre, incluso en momentos difíciles, por creer en mí, ahora y siempre, haciendo de mí la persona que soy hoy. A mi madre a quien este trabajo tiene una dedicación especial, por ser una fuente de inspiración. A Pedro mi pareja, por la paciencia y horas dedicadas, por el amor y por hacerme ver que lo imposible es posible, a mi hijo Tomás por su alegría, sus mimos y comprensión, y por ayudarme a ser la mujer que soy, y al que viene de camino por estar conmigo 24/7 aguantando la recta final de este proceso.

A mi familia elegida, mis amigos, por su amabilidad, su apoyo moral, por todos los momentos fantásticos y la relativización colectiva de los problemas. A Isabel Fernández, amiga, neuróloga y estadística, gracias por tu brillantez, acompañamiento y guiarme hacia soluciones inconcebibles. A Anna Giménez por ser una mentora además de una amiga y por iluminarme en la oscuridad, por mil momentos compartidos y muchos por venir. A Maite por su amistad genuina.

A mi equipo del CSMA del Clínic, por su apoyo incondicional durante los años de realización de esta tesis, por acompañarme en la dura labor, contra vientos y mareas, en paralelo con la actividad asistencial incesante, una pandemia, un embarazo y tantas otras cosas, por estar ahí para apoyarme y alentarme a seguir incluso en los momentos más difíciles. A Noelia, Paqui, Angie, Marga y los demás administrativos por vuestra sonrisa y apoyo. A Victoria Ruiz y Yudith Rivas por su buen humor, amabilidad y disponibilidad constante para ayudar y

colaborar en todo. A los compañeros psiquiatras, por su trabajo diario, a veces oculto pero magnífico, a Clemente García especialmente por sus recomendaciones y por guiarme en momentos difíciles, simplificando lo difícil, a Myriam por la paciencia y por la fuerza que siempre me ha dado, así como por la insistencia en que persistiera en este esfuerzo que significa concluir una tesis. A Marc, por las sonrisas, tranquilidad y conocimiento clínico. A Toni, por el enfoque didáctico y riguroso. A Iría, por su pragmatismo. A Víctor Navarro por todos sus enseñamientos. A Andrea Murru por la pasión por la investigación que contagia. A Lidia Ilzarbe por su practicidad. A José Goikolea por su sabiduría. A Jordi Blanch, por el optimismo, cercanía, fuerza, pasión y generosidad. A todos por derivarme pacientes y por su apoyo. Al equipo de psicología, por tener siempre las palabras adecuadas, especialmente a Amadeu por ser un amigo verdadero siempre presente, a Ivette por la disponibilidad y entusiasmo clínico y didáctico y a los demás por vuestra labor. Un agradecimiento también al equipo de trabajo social por ser tan necesario e indispensable. Finalmente, un agradecimiento a Anabel y a todo el equipo de trastorno bipolar, tanto clínico como de investigación, a los del CSMA, a los de la 9.0 a los de mallorca y a los demás, gracias por ser un equipo fantástico con una sed incesante de conocimiento y curiosidad eterna, por diseñar y rediseñar el futuro de tantos pacientes con trastorno bipolar en el mundo.

Al Dr. José Manuel Jara por ser mi primera e inolvidable fuente de inspiración para ser psiquiatra. A mi pediatra nutricional de infancia que desde pequeña me marcó con la importancia de un abordaje holístico e integrado, considerando la intervención nutricional como un pilar terapéutico fundamental.

Al equipo de Geelong, por su más cálida bienvenida. A Michael, por su manera amable, alegre e irónica de ver las cosas, por ser una persona brillante, próxima y humilde, un ejemplo de genialidad con el que ha sido un inmenso placer compartir meses de conocimiento y experiencias. A Felice Jacka por ser una pionera en el ámbito de la psiquiatría nutricional, desbravando terrenos fascinantes y otorgando a esta disciplina su merecido reconocimiento científico. A Wolf Marx por su incansable apoyo, y a todo el demás equipo por proporcionarme una experiencia de vida y académica maravillosa en Australia.

Al equipo de atención primaria. Al equipo de la unidad de hospitalización domiciliaria, por su labor nómada itinerante. A Marina, por poder afrontarlo todo. A Isa y Noel, por hacer siempre más de lo necesario, por creer en su trabajo y vivirlo con pasión. Al equipo de la unidad de hospitalización de agudos, por su trabajo tan exigente y en ocasiones turbulento.

A los residentes mayores, pequeños, rotantes externos y a mis co-R, Mireia y Pablo por hacer de la residencia y de los años de doctorado una experiencia inolvidable. Gracias Clara por haber estado siempre ahí desde los primeros días de mi vida de residente, a Nuria por su buen corazón y a Laia por su radiante sonrisa. A Gerard, a Cristian, a Néstor y a tantos otros por mencionar.

A todos mis compañeros de estos años y los que vendrán. A mis actuales compañeros del CSMA de Sant Andreu, a Tito, por su buena disposición, a Meri, Mari, Clemente y Conxi por ser un equipo de enfermería fantástico, a Tamara por su disponibilidad, a Cleris por ser como es y a Sara por su comprensión. A los demás psiquiatras, al equipo de PADI, psicología, trabajo social, administrativo, informática y de dirección, por en tan poco tiempo haberme adoptado y hacerme sentir en casa, valorada y capaz de seguir proyectos futuros con vuestro apoyo.

A mi Hospital, a mi Departamento, a mi Unidad, a mis CSMA's por siempre facilitar las cosas para que esto sea posible.

A todos los pacientes, por su generosa contribución a la investigación en tiempos difíciles y generalmente sin retorno inmediato, por su tiempo y fe en nosotros, y por su paciencia. Este, y todos los trabajos futuros, tratarán de ayudarles. A los familiares de los pacientes, por su papel fundamental y no reconocido.

A todos los trabajadores de la salud que no están específicamente mencionados aquí, pero que con su aporte hicieron posible este trabajo (personal médico, personal de enfermería, auxiliares de enfermería, administrativos, gerencia, personal de limpieza, seguridad, apoyo logístico, etc.). A la banda sonora que me acompañó. Gracias a todos y cada uno!

Financiación

Esta tesis doctoral se ha desarrollado en la Unidad de Trastornos Bipolares y Depresivos del Hospital Clínic de Barcelona, en el Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS) y en el centro de salud mental de la Esquerra del Eixample.

La investigación de la doctoranda ha contado con una beca “Premi fi de residència Emili Letang de l'Hospital Clinic de Barcelona”.

El proyecto no ha recibido otras fuentes de financiación.

Índice

Lista de abreviaturas y acrónimos.....	11
Enumeración de los artículos de la tesis	12
Resumen de la tesis	13
1. Introducción.....	16
Trastorno Bipolar	16
Definición y etiología.....	16
Clasificación y diagnóstico	18
Epidemiología.....	20
Curso y evolución	21
Comorbilidad médica	23
Prevalencia de problemas cardiovasculares y trastornos metabólicos e impacto en curso de enfermedad.....	23
Reducción de la esperanza de vida	27
Factores de riesgo para problemas de salud física en pacientes con TB	28
Hábitos de estilo de vida en el paciente con Trastorno Bipolar	31
Dieta	31
Ejercicio	33
Otros hábitos de estilo de vida, como descanso o consumo de tóxicos.....	35
Factores del estilo de vida e influencia en el pronóstico.	35
Tratamiento farmacológico y sus implicaciones	35
Psiquiatría nutricional y del estilo de vida	37
Psiquiatría nutricional	37
Psiquiatría del estilo de vida	38
Microbiota.....	39
Psiconeuroinmunoendocrinología	40
Intervenciones nutricionales y sobre el estilo de vida en TB.	41
Intervenciones dietéticas-nutricionales.....	41
Intervenciones de ejercicio	43
Intervenciones conjuntas o sobre estilo de vida.....	44
2. Hipótesis.....	58
Hipótesis primarias	58
Hipótesis secundarias.....	58
3. Objetivos	59
Objetivos primarios.....	59
Objetivos secundarios	59

4. Material, métodos y resultados.....	60
Artículo I.....	60
Artículo II.....	75
5. Discusión	89
Discusión general.....	89
Caracterización de la población a estudio, en cuanto a hábitos de estilo de vida, parámetros clínicos y metabólicos.	90
Parámetros clínicos	90
Parámetros metabólicos	91
Hábitos de estilo de vida	91
Relación entre los hábitos de estilo de vida, patrones dietéticos y tratamientos farmacológicos con parámetros metabólicos y el curso de la enfermedad en pacientes con TB.	92
Hábitos de estilo de vida, patrones dietéticos y su impacto a nivel clínico y metabólico	92
Tratamiento farmacológico y su impacto a nivel clínico y metabólico	93
Cambio de peso en pacientes en tratamiento con litio	94
Cambio de peso con litio	94
Cambio de peso con litio en comparación con alternativas terapéuticas	95
Cambio de peso con litio en comparación con placebo.....	96
Limitaciones y fortalezas	97
Implicaciones clínicas	99
Futuras líneas de investigación	100
6. Conclusiones	102
7. Bibliografía	104

Lista de abreviaturas y acrónimos

TB – trastorno bipolar

TB I – trastorno bipolar tipo I

TB II - trastorno bipolar tipo II

IMC – índice de masa corporal

ECV - enfermedades cardiovasculares

BDNF - brain derived neurotrophic factor

GSK-3 - Glycogen synthase kinase-3

HPA - hipotálamo pituitaria adrenal

SMILES - Supporting the Modification of lifestyle in Lowered Emotional States

Enumeración de los artículos de la tesis

Tesis en formato de compendio de publicaciones. La tesis consta de 2 objetivos primarios, 3 objetivos secundarios y 2 artículos.

Según los requisitos, los dos artículos son artículos originales publicados con autoría de la doctoranda dentro de los dos primeros cuartiles del campo **(Estudio I y II)**. Otra publicación indexada, perteneciente a esta línea de investigación se cita en las secciones de Introducción y Discusión de esta tesis como antecedentes e información complementaria de los estudios incluidos.

Las publicaciones indexadas directamente relacionadas con el proyecto de tesis se enumeran a continuación ordenadas por fecha de publicación ascendente, y en negrita paréntesis el número de estudio determinado por orden de secuencia temática:

1. **Gomes-da-Costa S**, Marx W, Corponi F, Anmella G, Murru A, Pons-Cabrera MT, Giménez-Palomo A, Gutiérrez-Arango F, Llach CD, Figo G, Kotzalidis GD, Verdolini N, Valentí M, Berk M, Vieta E, Pacchiarotti I. Lithium therapy and weight change in people with bipolar disorder: A systematic review and meta-analysis. *Neurosci Biobehav Rev.* (2022); 134:104266.

(Estudio II)

Factor de impacto; Quartil (JCR 2022): 8.2; Q1.

2. **Gomes-da-Costa S**, Fernández-Pérez I, Borrás R, Lopez N, Rivas Y, Ruiz V, Pons-Cabrera MP, Giménez-Palomo A, Anmella G, Valentí M, Berk M, Vieta E, Pacchiarotti I. Is a vegetarian diet beneficial for bipolar disorder? Relationship between dietary patterns, exercise and pharmacological treatments with metabolic syndrome and course of disease in bipolar disorder. *Acta Psychiatr Scand.* (2024); 150(4):209-22.

(Estudio I)

Factor de impacto; Quartil (JCR 2023): 5.3; Q1.

Resumen de la tesis

Título: Psiquiatría nutricional aplicada al trastorno bipolar

Introducción: El trastorno bipolar (TB) es un trastorno crónico del estado de ánimo caracterizado por fluctuaciones del estado de ánimo, que afecta a un amplio rango de población y se relaciona con un importante deterioro funcional y discapacidad, siendo la sexta causa de discapacidad en el mundo. Puede conducir a una afectación funcional importante y se relaciona con tasas de mortalidad aumentadas, especialmente debido a suicidio y enfermedades cardiovasculares. Su control es hoy en día insatisfactorio con los tratamientos habituales, que por otro lado también pueden contribuir a problemas de salud física como alteraciones metabólicas, para las que esta población ya es per se más proclive. En este contexto, la rama de la psiquiatría nutricional trata de buscar respuestas a estos problemas, testando el impacto de la dieta y como ésta se puede usar como abordaje complementario al tratamiento habitual, en pacientes con TB, con el objetivo de mejorar tanto la salud física como mental de esta población, minimizando el impacto metabólico del tratamiento farmacológico e incluso mejorando la adherencia terapéutica, funcionamiento global y calidad de vida percibida.

Hipótesis:

Se espera que, en pacientes con TB, seguir un estilo de vida de mayor calidad, en términos de más ejercicio y una dieta más saludable, se asociará con una menor severidad clínica (menos episodios, menor duración de la enfermedad, menos síntomas depresivos) y un mejor perfil metabólico (**estudio I**); además, diferentes tratamientos farmacológicos utilizados podrán variar de forma relevante en su impacto metabólico (**estudio I**). En concreto, con respecto al litio, se anticipa que éste puede contribuir moderadamente a un aumento de peso, aunque en menor medida que otras alternativas terapéuticas, con un perfil metabólico más favorable (**estudio II**).

Objetivos:

El objetivo principal de esta tesis es caracterizar una muestra representativa de nuestra población con TB, en fase de eutimia o con sintomatología depresiva leve, y evaluar el impacto de varios factores como la dieta, ejercicio y tratamiento farmacológico en el curso evolutivo de la enfermedad y su impacto metabólico (**estudio I**). Además, esta tesis tiene como uno de los objetivos principales establecer la evidencia existente sobre el impacto concreto del litio, uno de uno de los principales tratamientos utilizados en el TB, en el aumento de peso de estos pacientes (**estudio II**). Entre los objetivos secundarios están evaluar los patrones dietéticos de nuestra muestra, con análisis factorial, para caracterizar hábitos dietéticos y examinar sus implicaciones clínicas y metabólicas (**estudio I**); investigar la relación de los tratamientos farmacológicos en nuestra muestra con los parámetros metabólicos (**estudio I**) y comparar el efecto sobre aumento ponderal entre litio, placebo u otros comparadores activos (**estudio II**).

Métodos:

En función de cada estudio se han utilizado diferentes métodos. En el **estudio I** se ha realizado un estudio observacional transversal y en el **estudio II** se ha realizado una revisión sistemática y metaanálisis.

Resultados:

En el **estudio I** se ha identificado una elevada prevalencia de síndrome metabólico y obesidad, un funcionamiento global interferido y una baja adherencia a hábitos saludables de dieta y ejercicio físico. Se ha descrito un impacto positivo de la adherencia a dieta mediterránea a nivel de calidad de vida percibida, y de cantidad de ejercicio físico o consumo de frutos secos en determinados parámetros metabólicos. En cuanto al análisis de patrones dietéticos, se han descrito 3 patrones principales en nuestra muestra: “Western”, “omnívoro” y “vegetariano”, encontrándose asociaciones positivas del patrón vegetariano con variables psiquiátricas y metabólicas. Finalmente, en el **estudio I** se ha encontrado que el tratamiento con litio presentaba un perfil metabólico más favorable en comparación con otras alternativas (antipsicóticos o ácido valproico), lo que se ha confirmado en el **estudio II**, que ha resaltado el perfil más favorable del litio en comparación con los comparadores activos estudiados, de forma estadísticamente significativa. El tratamiento con litio se asoció a una tendencia al aumento de peso, no estadísticamente significativa de menos de 500g, más elevada en

estudios cortos, y sin identificarse diferencias significativas con el grupo placebo, en el que también se observó tendencia al aumento de peso sin alcanzar significación estadística, posiblemente derivada de una vulnerabilidad intrínseca y multifactorial de estos pacientes.

Conclusiones:

La monitorización de la salud metabólica en estos pacientes es fundamental, por la alta prevalencia de alteraciones metabólicas, así como una exploración de los hábitos de estilo de vida, dada la baja adherencia a hábitos saludables en esta población y el impacto positivo de éstos. El patrón de dieta vegetariana podría ser beneficioso para pacientes con TB por su doble impacto positivo tanto a nivel de salud mental como física, por lo que en un futuro se abrirían líneas de investigación a estudios controlados para investigar esta asociación. Algunos de los tratamientos farmacológicos utilizados son más proclives a agravar problemas metabólicos y de salud física, por lo que esto ha de ser un punto que valorar en la toma de decisiones terapéuticas, y en este sentido el litio, uno de los principales tratamientos del TB ha mostrado un perfil metabólico favorable, lo cual puede ayudar en la práctica clínica a una toma de decisiones informada tanto para terapeutas como pacientes. Finalmente, el desarrollo de programas de intervención sobre hábitos de estilo de vida se abre como una herramienta terapéutica complementaria, al tener una influencia positiva en la evolución de los síntomas psiquiátricos del TB, previniendo o minimizando problemas de salud física e incluso mejorando la adherencia al tratamiento farmacológico, reduciendo efectos secundarios asociados.

1. Introducción

Trastorno Bipolar

Definición y etiología

Durante la vida diaria, es común presentar fluctuaciones anímicas reactivas a factores externos, tanto estresantes como placenteros. Cuando estos cambios son de una intensidad significativa y persistentes en el tiempo, asociándose a cambios conductuales, afectación psicológica importante, alteración cognitiva, conduciendo finalmente a una afectación funcional global, se puede tratar de un trastorno afectivo subyacente.(1,2)

Los trastornos afectivos se clasifican en un espectro que va desde los trastornos depresivos unipolares hasta las diferentes categorías de trastorno bipolar. La principal característica que separa los trastornos bipolares de otros trastornos afectivos es la presencia de episodios maníacos o hipomaníacos recurrentes que pueden alternarse entre sí con episodios depresivos.(1)

Los trastornos bipolares incluyen varios trastornos de las emociones, la energía y el pensamiento que se caracterizan por episodios bifásicos de manía o hipomanía y depresión y se expresan como episodios recurrentes de cambios en los niveles de energía y el comportamiento. Los síntomas cognitivos son muy prevalentes en los pacientes y contribuyen en gran parte a la discapacidad asociada.(2,3)

Durante los episodios maníacos, la hiperactividad, el aumento de la autoestima, la grandiosidad, la reducción de la necesidad de dormir, el estado de ánimo y el comportamiento expansivos y los síntomas psicóticos son comunes, mientras que, durante los episodios depresivos, la disminución de la energía, la tristeza, el retraimiento social, la hipersomnia y la baja autoestima son los factores cardinales.(4)

Los síntomas psicóticos también pueden ocurrir durante episodios depresivos, pero se observan con mayor frecuencia durante la manía; concretamente, se presentan hasta en un 75% de los episodios maníacos mediante síntomas como delirios y alucinaciones, los cuales

pueden comprometer gravemente el funcionamiento psicosocial, hasta el punto de requerir hospitalización.(1)

La hipomanía es una forma de manía más leve y breve, en que el juicio de realidad se encuentra relativamente intacto. A menudo, los episodios agudos de alteraciones del estado de ánimo pueden incluir síntomas en ambos polos (es decir, síntomas mixtos).

Los pacientes con trastornos bipolares podrían lograr una remisión completa y tener períodos libres de síntomas, durante los cuales se supone que el trastorno está latente, con un tratamiento óptimo. Sin embargo, en muchos casos, los síntomas residuales persisten de manera generalizada, lo cual dificulta la recuperación funcional, especialmente después del segundo, tercer episodios y posteriores.(4)

En cuanto a la patogénesis, se conoce que es una enfermedad con una elevada tasa de heredabilidad, de entre 70-90%, siendo una de las más altas entre los trastornos psiquiátricos;(5) aun teniendo esto en cuenta, se considera que el modelo que mejor se aplica a esta enfermedad es un modelo multifactorial, donde se encuentran implicados factores genéticos y ambientales.(6) Actualmente, las variantes genéticas identificadas no se pueden utilizar a nivel clínico para predecir riesgo individual, curso evolutivo o respuesta a tratamiento. Varios factores ambientales han sido identificados como un factor de riesgo importante tanto para el debut de la enfermedad como para su curso evolutivo, tal como factores de riesgo en etapa perinatal,(7) el trauma infantil, el consumo de sustancias, u otros factores ambientales como cambios de estación o exposición a luz solar, bien conocidos por su influencia en el curso de esta enfermedad.(8) Se ha postulado una hipótesis denominada "kindling" como modelo para explicar la sensibilización gradual al estrés que conduce a episodios afectivos recurrentes.(9) En este modelo, el primer episodio de trastorno bipolar ocurre después de la exposición a un factor estresante, y los episodios posteriores pueden ocurrir sin exposición a un evento estresante identificable. Los mecanismos que sustentan la hipótesis del "kindling" pueden verse reforzados si la enfermedad no se trata o si la persona está expuesta a sustancias psicoactivas o a determinados hábitos de estilo de vida, como fumar o sedentarismo, los cuales ocurren con mayor frecuencia entre las personas con trastorno bipolar que en la población general.(1,10)

A nivel fisiopatológico, varios mecanismos se han hipotetizado. Históricamente se consideraba que los trastornos afectivos se debían a un desequilibrio en los sistemas de neurotransmisión monoaminérgicos.(1) Otro eje estudiado como potencialmente asociado a esta enfermedad ha sido el eje neuroendocrino, particularmente el hipotalámico-pituitario-tiroideo y el hipotalámico-pituitaria-adrenal. Más recientemente han surgido estudios sobre la importancia de la disfunción mitocondrial en la génesis del TB,(11,12) así como estudios sobre la modulación sináptica y plasticidad cerebral en determinadas regiones del cerebro de pacientes con TB, como el córtex prefrontal, hipocampo, amígdala y otras regiones del sistema límbico.(11,13)

Además, las alteraciones en la composición o concentración de la microbiota intestinal también podrían activar procesos inmunoinflamatorios,(14) cambios en la permeabilidad de la membrana neuronal y estrés oxidativo, relacionados con la fisiología del TB.(15,16) En una revisión sistemática reciente sobre microbiota en TB, los hallazgos más destacados sugieren que la baja diversidad α y la disbiosis con respecto a la abundancia de *Faecalibacterium* y *Bacteroides* pueden caracterizar el TB. La disminución de la riqueza y la producción de butirato también fomentarían la inflamación, que puede ser una parte hasta ahora poco reconocida de la fisiopatología subyacente al TB.(17)

Clasificación y diagnóstico

Los trastornos bipolares se han clasificado tradicionalmente como parte del espectro de las psicosis (especialmente como parte del extremo más grave del espectro, que corresponde al concepto clásico de psicosis maníaco-depresiva) o como un trastorno del estado de ánimo (un trastorno afectivo), potencialmente como un continuo desde la depresión unipolar hasta la enfermedad bipolar.(4)

El *Manual diagnóstico y estadístico de los trastornos mentales, quinta edición* (DSM-5)(18) creó una categoría para "trastornos bipolares y relacionados"; por tanto, los trastornos bipolares no se clasifican ni en trastornos psicóticos ni en trastornos afectivos. En el DSM-5, los trastornos bipolares se subclasifican en trastorno bipolar I, trastorno bipolar II, ciclotimia

y categorías residuales de formas atípicas que no encajan en los subtipos mencionados anteriormente. Esta subclasificación depende de la gravedad y la duración de los episodios maníacos (o hipomaníacos) y depresivos.(4) La *Clasificación Internacional de Enfermedades publicada recientemente, 11.ª revisión* (CIE-11) también incluye una sección sobre trastornos bipolares.(19)

El trastorno bipolar tipo I (TB I) se define por la presencia de episodios maníacos con una variedad de manifestaciones, incluyendo exceso de confianza, grandiosidad, locuacidad, desinhibición extrema, irritabilidad, disminución de la necesidad de dormir, y estado de ánimo muy elevado. Los síntomas psicóticos, como delirios y alucinaciones, se pueden producir tanto durante episodios depresivos como maníacos, aunque son más frecuentes en los episodios maníacos, y pueden comprometer el funcionamiento psicosocial hasta el punto de requerir hospitalización. A menudo, los episodios agudos de alteraciones del estado de ánimo pueden incluir síntomas en ambos polos (es decir, síntomas mixtos). El trastorno bipolar tipo II (TB II) se caracteriza principalmente por episodios de depresión alternados con hipomanía en lugar de manía. La presencia de al menos un episodio hipomaníaco se considera compatible con el diagnóstico de TB II. El trastorno ciclotímico se caracteriza por síntomas depresivos recurrentes y estados hipomaníacos, que duran al menos 2 años, que no cumplen con los criterios diagnósticos umbral para TB I o TB II. En las categorías residuales, nos encontramos “otro trastorno bipolar y trastorno relacionado especificado” en que se incluyen condiciones “bipolar like” que no cumplen criterios para TB I, TB II o ciclotimia, por insuficiente duración o severidad, tales como episodios hipomaníacos de corta duración con trastorno depresivo mayor, episodios hipomaníacos con síntomas insuficientes y presencia de trastorno depresivo mayor, episodio hipomaníaco sin antecedentes de trastorno depresivo mayor, o ciclotimia de corta duración. Asimismo, se establece la categoría del “trastorno bipolar y trastorno relacionado no especificado” cuando síntomas característicos del espectro bipolar no se ajustan a los diagnósticos previos. Finalmente existen otras dos categorías clasificatorias que incluyen “trastorno bipolar y trastorno relacionado inducido por sustancias/medicamentos” cuando diversos agentes tóxicos, sustancias o medicamentos, así como el alcohol, pueden generar el desarrollo de algún trastorno bipolar o trastornos relacionados como consecuencia, y “trastorno bipolar y trastorno relacionado debido a otra afección médica” cuando los síntomas característicos del trastorno bipolar y trastornos

relacionados como un estado de ánimo eufórico, expansivo e irritable, son consecuencia de alguna enfermedad o afección médica.(2)

A nivel de diagnóstico, éste se suele retrasar varios años, siendo la media de retraso entre el inicio de la enfermedad y el diagnóstico de unos 5-10 años.(20) Esto se debe a que los episodios depresivos suelen ser similares tanto en un trastorno depresivo unipolar como bipolar, salvo que en el TB son más frecuentes las características mixtas.(21,22) Asimismo los pacientes suelen reconocer más fácilmente los episodios depresivos que los hipomaníacos, lo que dificulta el diagnóstico si no se hace una anamnesis y entrevista enfocada y dirigida. Existen diferentes herramientas como escalas y tests de cribado,(23) pero la entrevista tanto al paciente como a familiares o acompañantes, con evaluación longitudinal de su curso de enfermedad, suele ser fundamental para un correcto diagnóstico, de crítica importancia para un correcto tratamiento.(4)

Epidemiología

La prevalencia estimada a lo largo de la vida es del 0,6 % para el TB I, del 0,4 % para el TB II, del 1,4 % para las manifestaciones subsindrómicas de los trastornos bipolares y del 2,4 % para el espectro bipolar más amplio de los trastornos bipolares.(24) Pese a estos datos, hay estudios que hipotetizan el infradiagnóstico tanto a nivel de atención primaria,(25) como en relación a pacientes tratados por episodio depresivo unipolar, incorrectamente diagnosticados, que podrían cumplir criterios para TB con las consecuencias que eso implicaría.(26) La prevalencia para TB I es similar independientemente del género, pero el TB II es más frecuente en mujeres.(27) La edad de inicio suele ser temprana, lo que tiene importantes implicaciones para el pronóstico y afectación funcional, ya que afecta a jóvenes en etapas vitales cruciales a nivel social así como de desarrollo académico profesional. Históricamente, se ha considerado que el TB presenta un inicio típicamente en edad joven, alrededor de los 20 años, y que un inicio temprano se suele asociar a un peor pronóstico.(4) No obstante, y considerando el infradiagnóstico detectado en varios estudios así como el período de latencia entre el inicio de la enfermedad y el diagnóstico de la misma, recientes trabajos postulan un modelo de presentación en 3 niveles, considerando un grupo de inicio

temprano, inicio medio e inicio tardío de la enfermedad, lo que podría tener implicaciones tanto a nivel pronóstico como terapéutico.(28)

A nivel de carga de la enfermedad, el TB se ha clasificado como la 17ª causa de discapacidad a nivel mundial, entre todas las enfermedades.(29) Teniendo en cuenta que se trata de una enfermedad crónica, se ha de considerar también la importante carga familiar que supone la enfermedad,(30) aparte de la carga económica tanto en términos de costes relacionados con la discapacidad como relacionados con los gastos directos en atención médica, que se podrían reducir con un diagnóstico temprano y correcto.(31,32)

A nivel epidemiológico, es aún importante considerar que se trata de una enfermedad asociada con elevadas tasas de comportamientos suicidas, comorbilidad con otra patología psiquiátrica y comorbilidad médica, lo que aumenta todavía más la carga global asociada a la enfermedad.(1)

Curso y evolución

Los pacientes con TB pueden alcanzar remisión del trastorno, asumiéndose como latente, con un manejo adecuado. No obstante, las recurrencias son habituales, particularmente si la adherencia al tratamiento es pobre. Asimismo, síntomas residuales y subsindrómicos persisten de manera generalizada en muchos pacientes, lo que dificulta la recuperación funcional.(4) El índice de polaridad puede predecir la polaridad de episodios subsecuentes, lo que también tiene implicaciones a nivel terapéutico y pronóstico.(2)

Un inicio temprano de la enfermedad se asocia a peor pronóstico, tanto por mayor retraso en el diagnóstico, como por la afectación funcional a edad temprana, episodios depresivos más severos o comorbilidad con otros problemas psiquiátricos aumentada.(33) Para la mayoría de las personas con TB I o II, los episodios depresivos duran considerablemente más que los episodios maníacos o hipomaníacos a lo largo del curso de la enfermedad, y la depresión bipolar representa la mayor parte de la morbilidad y mortalidad de la enfermedad.(34,35)

El deterioro funcional se debe a diferentes factores como fases agudas y síntomas residuales o afectación cognitiva,(36,37) siendo que el deterioro cognitivo afecta a una proporción sustancial de adultos eutímicos con TB, lo que contribuye a un deterioro funcional y una reducción de la calidad de vida.(3,38) También los efectos secundarios del tratamiento pueden contribuir al deterioro funcional. Tal como comentado previamente, el deterioro funcional global observado en esta población, que afecta principalmente a una población económicamente activa, se asocia a una elevada carga para la sociedad.(39,40)

El tratamiento del TB implica tratamientos farmacológicos y no farmacológicos para las fases agudas de los episodios maníacos (o hipomaníacos) y depresivos, y terapia a largo plazo para prevenir la recurrencia de episodios.(41,42) El tratamiento farmacológico de la depresión bipolar consiste principalmente en combinaciones de al menos dos fármacos, incluyendo estabilizadores del estado de ánimo (litio y anticonvulsivos), antipsicóticos atípicos y antidepresivos.(43–45) Las respuestas insatisfactorias a los tratamientos disponibles para el trastorno bipolar son muy frecuentes, especialmente para la depresión bipolar, y la regla es el uso empírico de diversas combinaciones de tratamientos, en gran medida no probados.(46)

A pesar de las terapias disponibles para los trastornos bipolares, el tratamiento pierde eficacia cuando la adherencia es incierta. Por lo tanto, mejorar la adherencia es una de las piedras angulares en el manejo de los pacientes con trastornos bipolares. Además, es esencial equilibrar la eficacia y la seguridad a corto y largo plazo de todos los fármacos en pacientes con trastorno bipolar, por lo que es importante la caracterización clínica del paciente adulto con trastorno bipolar, con el objetivo de la personalización del manejo.(47)

Los tratamientos farmacológicos disponibles pueden presentar diferentes efectos secundarios; entre ellos, los tratamientos antipsicóticos, ampliamente utilizados tanto en el episodio agudo como en el tratamiento de mantenimiento, se asocian con el aumento de peso y alteraciones a nivel metabólico.(48,49) Algunos de los estabilizadores del estado de ánimo también se asocian con riesgo aumentado de presentar aumento de peso;(50) no obstante, el efecto del litio, uno de los tratamientos más importantes en el TB, sobre el aumento de peso no está claro, con algunos trabajos indicando el aumento de peso como un efecto secundario potencial.(51)

Comorbilidad médica

El trastorno bipolar se asocia con una importante comorbilidad médica, especialmente problemas cardiovasculares, y con una esperanza de vida reducida. En relación a la comorbilidad médica, algunos de los problemas altamente prevalentes incluyen diagnósticos como diabetes mellitus, síndrome metabólico, obesidad, migraña, osteoporosis, fibromialgia, así como otros problemas endocrinológicos y cardiovasculares.(1) Esto se asocia con una peor salud física pero también puede impactar negativamente en el propio curso de la enfermedad mental.

Prevalencia de problemas cardiovasculares y desórdenes metabólicos e impacto en curso de enfermedad.

Problemas cardiovasculares

Los problemas cardiovasculares son uno de los problemas comórbidos más importantes en los pacientes con TB, tanto por su elevada prevalencia como por el peso que tienen a nivel de una morbilidad aumentada en esta población. Las enfermedades cardiovasculares (ECV) incluyen cualquier enfermedad que afecta el sistema cardiovascular, siendo los principales componentes la enfermedad coronaria, cerebrovascular pero también la hipertensión entre otras. De acuerdo con las estadísticas de 2019 de la Organización Mundial de Salud, las ECV representan 17,9 millones o el 32% de todas las muertes mundiales. Asimismo, la prevalencia de ECV en pacientes con trastorno mental severo puede ser 2-3 veces superior a la población general, con algunos estudios describiendo un riesgo de mortalidad por ECV entre 35-250% más elevado en pacientes con TB que en población general.(52,53) Por otro lado la ECV puede ocurrir hasta 17 años antes en pacientes con TB que en la población general.(54)

A nivel etiopatogénico se pueden considerar factores de estilo de vida, tratamiento farmacológico y, a nivel genético, se ha observado un solapamiento poligénico entre la ECV y TB, lo que implica mecanismos genéticos moleculares compartidos. El riesgo aumentado que se observa en pacientes con TB de sufrir de ECV se debe justamente a una presencia elevada

de varios factores de riesgo de ECV, como son el tabaquismo, dislipemia, diabetes, hipertensión, obesidad y hábitos de estilo de vida poco saludables.(55) Algunos estudios describen el propio TB como un factor de riesgo independiente para sufrir ECV, después de controlar por diferentes factores de confusión.(55) Se han propuesto diferentes mecanismos biológicos que expliquen este hallazgo que incluyen inflamación sistémica, estrés oxidativo, reducción de BDNF (*brain derived neurotrophic factor*), aumento de hidróperóxido lipídico que se correspondería con un engrosamiento de la íntima de la carótida y diferentes genes.(11,56) Finalmente, se ha encontrado una asociación entre desarrollar factores de riesgo de ECV como síndrome metabólico, diabetes, etc., algunos de los que se detallarán a continuación, y una peor evolución del TB, con mayor tasa de refractariedad a tratamiento, más comorbilidades médicas asociadas y más gasto médico asociado.(55)

Diabetes

Según diferentes estudios la prevalencia de diabetes tipo 2 en pacientes con TB es superior a la observada en la población general, en torno al 8-17%.(57–59) También la glucosa alterada en ayunas mostró una elevada prevalencia en torno al 22%.(57) Varios mecanismos pueden estar implicados en una patogénesis compartida entre ambas enfermedades como son una disfunción del eje hipotálamo-pituitario-adrenal, la disfunción mitocondrial, desregulación de la GSK-3 (*Glycogen synthase kinase-3*), entre otros mecanismos.(60)

A nivel clínico del TB, se ha visto que padecer de diabetes tipo 2 puede tener implicaciones pronósticas importantes, presentando un curso con más tendencia a la cronicidad, más ciclación rápida y mayor número de ingresos hospitalarios requeridos.(61) Asimismo, pacientes con TB y diabetes de forma comórbida reportan una peor calidad de vida percibida y funcionamiento global.(60) Finalmente, algunos estudios han demostrado un impacto a nivel cognitivo, por lo que sufrir diabetes podría ser considerado un factor de riesgo potencial para disfunción cognitiva en pacientes con TB.(62,63)

Por otro lado, padecer TB también podría repercutir negativamente en la evolución de la diabetes, al dificultar la adherencia tanto a tratamientos como pautas conductuales indicadas en esta enfermedad.(60)

Obesidad

La obesidad es otra comorbilidad importante, muy frecuente en este grupo de pacientes. Diferentes estudios han demostrado una prevalencia de obesidad superior en pacientes con TB en comparación con población general, de entre 21% y 49%, (52,57,64,65) pudiendo alcanzar los 69% si se considera obesidad y sobrepeso en global.(65)

En relación con los factores de riesgo para la coocurrencia de obesidad en pacientes con TB, el tratamiento farmacológico es un factor importante, aunque en estudios que incluyen pacientes no previamente tratados ya se observa una mayor prevalencia de obesidad que en pacientes con otros trastornos psiquiátricos. Asimismo, se ha encontrado en pacientes que solicitan cirugía bariátrica una elevada prevalencia de pacientes con trastornos del espectro bipolar.(66)

En su conjunto esto parece apuntar a que entre ambas condiciones hay un nexo de unión y mecanismos fisiopatológicos compartidos. Hay varias hipótesis que intentan explicar esta asociación entre obesidad y TB, como características fenomenológicas compartidas como son la alteración en la impulsividad, descanso nocturno y balance ingesta/gasto energético; alteraciones neurobiológicas compartidas en relación a la disfunción del eje HPA (hipotálamo pituitaria adrenal), sistemas de neurotransmisores, BDNF o a nivel de la leptina; o la relación entre la ingesta y el alivio de síntomas depresivos por liberación de dopamina, que puede contribuir a un círculo vicioso ya que los pacientes usan la ingesta como herramienta de alivio sintomático. Finalmente, a nivel genético y epigenético puede haber factores que predispongan a dicha comorbilidad.(66)

A nivel pronóstico, también se ha visto un impacto relevante en el curso de la enfermedad, y esto se podría dar por un efecto tóxico de la obesidad vía procesos proinflamatorios o por alteraciones de función insulínica. Los pacientes con TB y obesidad pueden tener unas alteraciones biológicas que conllevan peor pronóstico,(66) con más recurrencia de síntomas depresivos, mayor duración de los episodios agudos, puntuaciones más elevadas de depresión y menor tiempo de recaída que los pacientes no obesos.(65,67)

Otros estudios han encontrado que la obesidad se ha asociado con menor grado de mejoría sintomática, baja adherencia a tratamiento, peor funcionamiento, peor satisfacción vital percibida, más tendencias suicidas y mayor tendencia a ciclación rápida.(61,67,68) Por otro

lado, estudios recientes han encontrado datos contrarios en relación a la asociación entre obesidad e ideación suicida, sin encontrar relación con intentos de suicidio, y han reportado que los pacientes con peso normal presentaban mayor tendencia a ideación suicida que los pacientes con sobrepeso, no encontrándose relación de ideación suicida con pacientes obesos.(69)

A nivel cognitivo también se ha encontrado un impacto negativo de la obesidad en pacientes con TB, presentando una función cognitiva alterada, especialmente a nivel de funciones ejecutivas.(63,70) La presencia de obesidad en pacientes con depresión se relaciona con una tasa más elevada de síntomas atípicos y parece estar predominantemente asociada con un diagnóstico de TB (71–73). Finalmente, la presencia de obesidad se ha asociado a un riesgo superior de comorbilidad médica relacionada y mortalidad prematura.

Síndrome metabólico

Los estudios en población española muestran tasas de prevalencia de síndrome metabólico en la población diagnosticada de TB de alrededor del 22,4%-24,7%, significativamente más altas que en la población general (64,74). Otros estudios registran tasas incluso más elevadas de prevalencia hasta 31,7%-54% dependiendo de criterios utilizados o región geográfica.(75,76)

Tal como se ha descrito previamente, varios factores etiopatogénicos, de estilo de vida o predisposición genética podrían ser compartidos. Alteraciones en sistemas metabólico e inflamatorio podrían sugerir, como mecanismos biológicos comunes entre ambas patologías, una señalización glucocorticoide alterada, estrés oxidativo, desregulación autonómica y biosíntesis energética alterada.(77)

También se ha visto que la presencia de síndrome metabólico de forma comórbida puede implicar un peor pronóstico.(76) Estudios previos han demostrado que los pacientes con TB que sufren de síndrome metabólico requieren un mayor número de hospitalizaciones, pasan más tiempo en sintomatología depresiva, con más tendencia a presentar sintomatología maníaca como debut.(61) Asimismo, en relación al funcionamiento global y tendencias suicidas hay datos contradictorios, sin que esté claramente definida esta relación. (61,68,69)

A nivel cognitivo se ha observado que la presencia de componentes de síndrome metabólico puede afectar negativamente la función cognitiva de estos pacientes.(63)

Aparte de las comorbilidades médicas más frecuentes, tanto de origen cardiovascular como metabólica, algunas de ellas ya explicadas en detalle previamente, se pueden presentar otras comorbilidades importantes en diferentes ámbitos, digestivo, respiratorio, infeccioso. estomatológico, oncológico, musculoesquelético, urológico y ginecológico con mayor prevalencia que en la población general. Esto debe considerarse a nivel clínico, ya que es frecuente en estos pacientes que no se realiza una evaluación médica adecuada por una serie de circunstancias, lo que contribuye a una mortalidad prematura, exhaustivamente descrita en este grupo de pacientes.

En resumen, las complicaciones metabólicas se están asumiendo como una característica importante del TB, que podría contribuir a cierta tendencia refractaria al tratamiento.(60) En conjunto, este conocimiento resalta la importancia de identificar y tratar alteraciones metabólicas, con el objetivo de poder mejorar la evolución clínica y la respuesta al tratamiento, especialmente en pacientes refractarios.

Reducción de la esperanza de vida

Muchos trabajos han mostrado la asociación entre padecer un diagnóstico de trastorno mental severo incluyendo TB, esquizofrenia o trastorno esquizoafectivo, y un exceso de mortalidad, hasta 2-3 veces superior a las tasas de la población general, lo que se traduce en un acortamiento de esperanza de vida de 13 a 30 años, aun en países con un buen sistema de salud.(52,78)

Los pacientes con TB tienen un riesgo de muerte superior a la población general, tanto por causas no naturales, como suicidio o accidentes, como por causas naturales, responsables de la mayoría de exceso de mortalidad, por una alta prevalencia de problemas médicos comórbidos, lo que en conjunto conduce a una esperanza de vida reducida y mortalidad prematura.(53,79,80)

La tasa de suicidio combinada en el TB es de 164 por 100.000 años-persona, siendo según algunos trabajos 11 a 30 veces superior en pacientes con TB que en la población general.(1,78,81) Las personas con TB representan entre el 3,4 y el 14% de todas las muertes por suicidio, siendo el envenenamiento y el ahorcamiento los métodos más comunes. Los estudios epidemiológicos informan que entre el 23 y el 26% de las personas con trastorno bipolar intentan suicidarse,(81) y que sería expectable que cerca de un 15% de las personas con TB se mueran por suicidio.(78) Diferentes factores se han visto relacionados con una mayor tasa de suicidios, entre ellos: sexo, edad, raza, estado civil, afiliación religiosa, edad de inicio de la enfermedad, duración de la enfermedad, subtipo de trastorno bipolar, polaridad del primer episodio, polaridad del episodio actual/reciente, polaridad predominante, características del episodio del estado de ánimo, psicosis, comorbilidad psiquiátrica, características de la personalidad, disfunción sexual, antecedentes familiares de primer grado de suicidio o trastornos del estado de ánimo, intentos de suicidio pasados, trauma en los primeros años de vida y precipitantes psicosociales.(82)

En relación con la mortalidad por causas naturales se ha observado que la tasa de mortalidad por condiciones médicas específicas, como problemas cardiovasculares, endocrino/metabólicos y respiratorios, es claramente superior en pacientes con TB comparativamente a la población general, siendo los problemas cardiovasculares y respiratorios los que más contribuyen para este exceso de mortalidad.(53,83,84)

Factores de riesgo para problemas de salud física en pacientes con TB

Diferentes motivos se han postulado para el riesgo aumentado de sufrir de problemas de salud física, observado en pacientes con TB. Éstos se pueden dividir en factores de riesgo modificables del estilo de vida, factores biológicos, factores relacionados con la propia fenomenología y tratamiento del TB, factores relacionados con el sistema sanitario o socioeconómicos.(85)

Factores relacionados con estilo de vida

Factores de riesgo modificables como la dieta, ejercicio físico, consumo de tóxicos, etc., son clave para una elevada comorbilidad médica. Son pacientes que presentan tendencia al

sedentarismo, elevada ingesta de carbohidratos y azúcares, con una elevada comorbilidad de consumo de sustancias, especialmente tabaco, pero también otras.(86,87)

Factores biológicos

Hay factores genéticos y epigenéticos compartidos entre TB y problemas de salud física, y procesos fisiopatológicos comunes, como los efectos relacionados con el estrés en el sistema inmunitario y neuroinflamación (88) y en el eje hipotálamo-hipofisario, o el aumento de la actividad del sistema nervioso simpático.(53)

Factores relacionados con la fenomenología del trastorno

La propia fenomenología de los síntomas psiquiátricos puede explicar en parte ciertas conductas, que pueden conducir a un aumento de riesgo cardiovascular y problemas de salud física. Por ejemplo, los pacientes con TB pasan una gran parte de su vida en un estado depresivo o subdepresivo, lo que puede traducirse en una tendencia a alteración del equilibrio entre ingesta y gasto energético, con una tendencia a la obesidad como sucede por ejemplo en los síntomas atípicos de la depresión (hipersomnia, hiperfagia, enlentecimiento motor) que contribuyen a aumento de peso. La afectación cognitiva o de motivación observada en estos pacientes durante estados depresivos podría también contribuir a una dificultad añadida para planificar y mantener adecuadas rutinas, tanto dietéticas como de ejercicio.(89) También los problemas de sueño observados en los pacientes con TB, incluso en estados eutímicos, podrían explicar problemas de resistencia insulínica y las tasas aumentadas de diabetes en esta población.(60) Por otro lado, los estados maníacos pueden contribuir a una alimentación más desequilibrada, así como a un incremento de consumo de sustancias tóxicas.

Factores relacionados con tratamiento farmacológico

Los antipsicóticos y en menor medida los estabilizadores del estado de ánimo o los antidepresivos pueden contribuir a un riesgo aumentado de sufrir enfermedades físicas, incluyendo obesidad, dislipemia, diabetes mellitus, hiponatremia, problemas de tiroides, cardiovasculares, del tracto respiratorio o gastrointestinal, hematológicos, musculoesqueléticos o trastornos de movimiento. Las dosis altas de tratamiento, la

polifarmacia o el tratamiento de subpoblaciones especialmente vulnerables aumentan el riesgo de aparición de problemas físicos asociados.(85)

Asimismo, los efectos secundarios de la farmacoterapia en el metabolismo de la glucosa, en el perfil lipídico, el aumento de apetito o *craving* por carbohidratos también pueden contribuir a varios problemas metabólicos.(60,90)

Factores socioeconómicos

Otros factores que pueden contribuir a problemas de salud física son el acceso limitado a comida saludable por dificultades económicas, o barreras a nivel social, como la distorsión de la percepción de lo que serían hábitos de vida saludables, la dificultad de cambiar hábitos familiares o barreras a nivel cultural como pueden ser los hábitos de preparación de comida o un patrón dietético rico en comida procesada.(89,91)

Factores relacionados con el sistema sanitario

Se ha descrito un acceso reducido y poco efectivo a servicios de salud, actitudes sesgadas de los propios profesionales sanitarios, o una monitorización insuficiente de los problemas médicos o factores de riesgo cardiovasculares en pacientes con trastorno mental severo, tanto por parte de los profesionales de la red de salud mental como por sus médicos de atención primaria, lo que retrasa un adecuado diagnóstico y manejo de estos problemas conllevando un peor pronóstico, así como un aumento de la morbilidad y mortalidad. (52,53,92)

Existe evidencia que indica que las personas con enfermedades mentales graves tienen menor probabilidad de recibir niveles estándar de atención para la mayoría de problemas médicos.(52) Otros estudios han demostrado que el estigma y discriminación pueden ser responsables por disparidades en el abordaje cardiovascular de pacientes con trastorno mental severo, encontrándose que estos pacientes tienen considerablemente menos probabilidad de recibir tratamiento cardiovascular invasivo o una prevención secundaria adecuada, en comparación con la población general.(93)

Hábitos de estilo de vida en el paciente con Trastorno Bipolar

Dieta

Como expuesto anteriormente, esta población muestra una tendencia a peores hábitos alimentarios por muchas razones: la propia sintomatología puede condicionar la ingesta de alimentos y preferencias, el deterioro funcional dificulta la preparación de los alimentos, y en ocasiones otras barreras en el acceso a alimentos saludables, como problemas sociales o económicos.(89,94) En general pacientes con trastorno mental severo como esquizofrenia o TB presentan un consumo elevado de nutrientes obesogénicos o tendencia a dietas proinflamatorias.(95) Hábitos dietéticos pobres pueden aumentar la comorbilidad psiquiátrica y física, empeorar el funcionamiento psicosocial y cognitivo, y predecir una peor respuesta al tratamiento.(96) Un estado nutricional deficitario podría asimismo influenciar el curso de los ingresos hospitalarios, con una estancia más prolongada, algo especialmente relevante en una población en que pueden coocurrir la presencia de sobrepeso y malnutrición.(97)

Actualmente, existen numerosas evidencias observacionales en distintos países y grupos de edad que respaldan que la calidad de la dieta es un posible factor de riesgo o de protección para síntomas de depresión y/o ansiedad. Un metaanálisis confirmó que la adherencia a un patrón alimentario “saludable”, que incluye una mayor ingesta de frutas y verduras, pescado y cereales integrales, se asoció con una menor probabilidad de depresión en adultos.(98,99) Una revisión sistemática también encontró que la dieta mediterránea podría reducir los síntomas o la ocurrencia de ansiedad y depresión.(100) La ausencia de legumbres en la dieta, junto a un consumo reducido de frutas y verduras y elevado consumo de dulces y azúcares refinados, se ha asociado significativamente con depresión.(101) En otros estudios el consumo de frutos secos se ha visto asociado con una incidencia reducida de depresión. (102–105) Además, existen evidencias de que una dieta saludable como la dieta mediterránea puede reducir la incidencia de eventos cardiovasculares importantes, como se demostró en el estudio PREDIMED.(106). Varios estudios asocian una dieta poco saludable o “Western”, rica en harinas refinadas, carnes procesadas y dulces, a mayor incidencia de ansiedad o depresión así como otros problemas de salud física.(107)

En cuanto a patrones específicos de dieta estudiados en su impacto en la salud mental, uno de los más estudiados ha sido el consumo de la dieta mediterránea, pescado/omega 3 o dietas tradicionales. También se ha estudiado el efecto de la dieta vegetariana con resultados contradictorios a nivel de su influencia en síntomas psiquiátricos como ansiedad y depresión,(108) pero en general con un impacto positivo en problemas de salud física como diabetes, perfil lipídico u otros problemas cardiovasculares.(109)

En resumen, 5 recomendaciones dietéticas para la prevención de depresión emergen de la evidencia científica actual, las cuales contemplan 1) seguir una dieta “tradicional”, como podría ser la dieta mediterránea, noruega, japonesa, por ejemplo; 2) aumentar el consumo de frutas, verduras, legumbres, cereales integrales, frutos secos y semillas; 3) incluir en la dieta alimentos ricos en omega 3 o ácidos grasos poliinsaturados; 4) sustituir comidas poco saludables por alternativas más saludables; 5) limitar el consumo de comida procesada, “*fast-food*”, bollería comercial u otro tipo de dulces refinados.(110)

En el caso del TB, la evidencia es aún escasa, pero la dieta parece tener implicaciones potencialmente significativas en su evolución y tratamiento. La evidencia disponible sugiere que este subgrupo de pacientes tiene hábitos dietéticos más insanos, lo cual puede tener implicaciones terapéuticas importantes dada la elevada comorbilidad médica observada en estos pacientes, pudiendo la dieta tener un papel en el manejo y la prevención de varias enfermedades físicas altamente comórbidas, entre ellas la diabetes tipo 2, el síndrome metabólico, la obesidad y las enfermedades cardiovasculares. Por otro lado, se plantea que la dieta también puede influenciar diferentes procesos biológicos desregulados en el TB, como el sistema monoaminérgico, procesos inmunes/inflamatorios, el estrés oxidativo y la neuroprogresión, impactando en el pronóstico de la propia enfermedad psiquiátrica, además de en la comorbilidad física asociada. (94) Estudios más recientes han encontrado que las personas con TB presentaban de forma significativa un consumo más elevado de energía total, carbohidratos, proteína, azúcar, grasa total y grasa saturada que en la población general.(95)

Un estudio realizado sobre la calidad de la dieta y patrones alimentarios en pacientes eutímicos con TB encontró que estos pacientes presentaban peores hábitos dietéticos y menor adherencia a la dieta mediterránea en comparación con el grupo control, lo que enfatiza que la tendencia a una dieta poco saludable no es exclusiva de los períodos de inestabilidad afectiva, estando posiblemente presente en el transcurso de todo el proceso.(111)

Otro trabajo que estudió la influencia de suplementos nutricionales en el TB resaltó un efecto positivo en la mejoría de síntomas de TB con la ingesta o suplementación de ácidos grasos insaturados, especialmente omega 3, marisco, ácido fólico y zinc; con un efecto variable mayoritariamente con resultados no significativos con creatinina, carnitina, vitamina D, inositol o N-acetilcisteína; asimismo, mencionan resultados prometedores asociados con la suplementación con coenzima Q10 o probióticos.(112)

En un estudio reciente que evaluó el impacto de la calidad dietética en la diversidad de microbiota en pacientes recientemente diagnosticados de TB se han encontrado correlaciones positivas, por un efecto combinado de consumo de pescado, legumbres, frutas y frutos secos, encontrando una correlación inversa modulada por el consumo de alcohol y carnes procesadas, concluyendo que una dieta variada se asocia a diversidad de microbiota en estos pacientes.(113)

Ejercicio

El problema del sedentarismo en los pacientes con TB tal como la dieta es un área de creciente interés, no sólo por el impacto que puede tener en la salud física de estos pacientes, ya ampliamente discutida en las páginas previas, sino también por el impacto que puede tener en el pronóstico del propio TB, en la mejoría de síntomas depresivos, funcionamiento global y calidad de vida percibida,(114) y también dados los efectos fisiológicos cada vez más estudiados sobre neurogénesis e impacto en BDNF.(115)

Se han demostrado elevados niveles de sedentarismo durante el día en adultos con TB, siendo que las medidas de medición objetivas demuestran significativamente menores niveles de

ejercicio que con las medidas subjetivas, señalando que una mayor edad y mayor nivel de IMC se asocian a menores niveles de actividad física. (116) En un estudio que pretendía estudiar si los adultos con TB tenían mayor tendencia al sedentarismo que el grupo control utilizando medidas objetivas como acelerómetro esta hipótesis se confirmó, sugiriendo la importancia de intervenciones sobre el ejercicio físico como herramienta terapéutica tanto para los propios síntomas del TB como en la mejoría de calidad de vida o funcionamiento global, contribuyendo igualmente a reducir la comorbilidad médica de estos pacientes.(117)

En un estudio que investigaba la asociación del ejercicio con la calidad de vida y síntomas afectivos en pacientes con TB se reportó que un 40% de la muestra no realizaban ejercicio regular, con asociaciones entre ejercicio menos frecuente con mayor IMC, más síntomas depresivos y mayor duración de estos períodos, peor calidad de vida y funcionamiento global. Por otro lado la realización de ejercicio más frecuente se ha encontrado asociada a mayor tasa de síntomas maníacos.(118) En una meta-revisión reciente se ha encontrado evidencia para una relación inversa entre mayor realización de actividad física y menor riesgo de desarrollar TB. (119)

Recientemente en un trabajo publicado en la revista Cochrane se analizan los factores que pueden influenciar la participación en actividad física de los pacientes con TB. La vergüenza por la apariencia o el estigma por el diagnóstico de salud mental pueden tener un peso importante, también el poco hábito previo al diagnóstico a realizar ejercicio. Problemas de salud física u otros factores como el sobrepeso, la medicación, los hábitos tóxicos, dieta poco saludable y malos hábitos de descanso, entre otros, también podrían contribuir a la limitación en la realización de ejercicio físico por este grupo de pacientes. Otro factor limitante considerado es la falta de accesibilidad a centros deportivos, problemas en transporte o problemas económicos. Tampoco se fomenta la realización de ejercicio en las unidades de internamiento donde podría ser una buena oportunidad de trabajar estos hábitos. Estar estable anímicamente y motivado al cambio han sido descritos como factores promotores, tal como recibir apoyo tanto del círculo social como del equipo terapéutico y encontrar el tipo de ejercicio adecuado, que en muchos casos es caminar. Se ha visto que seguir una rutina de ejercicio equilibrada puede ayudar a manejar los síntomas afectivos, teniendo en cuenta que la falta de ejercicio o el exceso pueden ser perjudiciales para descompensaciones depresivas

o maníacas respectivamente, por lo que la monitorización del ejercicio incluso podría ser utilizada con valor predictivo de pródromos de recaídas. La realización de ejercicio de forma rutinaria podría ayudar a estructurar el día a día de estos pacientes, establecer relaciones sociales, perder peso, mejorar el perfil cardiovascular o mejorar la calidad de vida percibida. Pese a todo este conocimiento todavía pocos pacientes reciben educación sobre la importancia de la realización de ejercicio físico, lo cual remarca la importancia de formar los profesionales sanitarios en este sentido.(120)

Otros hábitos de estilo de vida, como descanso o consumo de tóxicos.

De forma no menos importante, se han encontrado asociaciones relevantes con otros hábitos de estilo de vida, no tan profundizados en el presente trabajo. En fumadores se encontró mayor tendencia a la depresión y a sufrir TB que en no fumadores. También los hábitos de descanso nocturno pueden tener un impacto importante en la evolución y pronóstico del TB. (119)

Factores del estilo de vida e influencia en el pronóstico.

En resumen, tanto los hábitos sedentarios como seguir una dieta poco saludable, entre otros hábitos de vida poco saludables, han demostrado evidencia de asociación con síntomas depresivos y un peor pronóstico, tanto de la enfermedad mental como física al ser factores de riesgo para comorbilidad física y problemas cardiovasculares, que a su vez también se relacionan con peor pronóstico de la enfermedad y mortalidad prematura.(121,122) Seguir unos hábitos saludables por otro lado, aparte de asociarse a un mejor pronóstico, sería predictor de mejor adherencia a tratamiento, lo que a su vez contribuye a una mejor evolución.(123)

Tratamiento farmacológico y sus implicaciones

El TB es un trastorno crónico que requiere tratamiento de mantenimiento, con al menos un agente psicofarmacológico, aunque en muchas ocasiones se requiere una combinación de diferentes tipos de fármacos.(44,124,125) El propio tratamiento farmacológico del TB se ha planteado en numerosas ocasiones como un factor de riesgo en sí mismo para problemas

metabólicos y de salud física,(85) dado el impacto metabólico que pueden tener muchos de los tratamientos utilizados,(90) lo que indirectamente también perjudica una adecuada adherencia terapéutica.

Los antipsicóticos son uno de los grupos farmacológicos más estudiados dado el importante impacto que pueden tener en el aumento de peso, metabolismo de la glucosa y perfil lipídico.(90) Los principales efectos adversos relatados con los antipsicóticos de segunda generación incluyen efectos metabólicos (aumento de peso, efectos en el metabolismo de la glucosa y prolactina), sedación, disfunción sexual y síntomas extrapiramidales (en menor medida que los antipsicóticos de primera generación). En este punto se ha de considerar que el perfil de efectos adversos y tolerabilidad puede variar mucho entre diferentes fármacos.(126) Hay una jerarquía en el riesgo de aumento de peso según el antipsicótico; entre los de segunda generación, los que más contribuyen a aumento de peso son olanzapina, clozapina, quetiapina, paliperidona y risperidona, mientras que otros presentan menor o escaso efecto sobre el aumento de peso, como ziprasidona, aripiprazol, lurasidona o cariprazina, entre otros. En relación a los antipsicóticos de primera generación, clorpromazina es de los que más efectos sobre el aumento de peso presenta.(85,127) Cabe considerarse que el aumento de peso suele ser más pronunciado en pacientes que reciben antipsicóticos por primera vez. (128) A nivel de la repercusión en alteración del metabolismo de la glucosa o perfil lipídico también el impacto es diferente según el fármaco, siendo olanzapina uno de los que presentan peor perfil y aripiprazol presentando un perfil más neutral.(90)

En relación con los estabilizadores del estado de ánimo la evidencia es más heterogénea, existiendo evidencia de la relación de tratamiento con ácido valproico y aumento de peso u otras alteraciones metabólicas, con menos estudios disponibles sobre el impacto del tratamiento con litio,(129) algunos sin encontrar una clara asociación con aumento de peso o problemas de metabolismo lipídico o de la glucosa,(130,131), y otros estudios que sugieren que el litio puede contribuir a aumento de peso aunque presentando un perfil más favorable que muchas de las alternativas farmacológicas como olanzapina, quetiapina o ácido valproico.(129) Otros grupos farmacológicos como carbamazepina, lamotrigina y topiramato, presentan menor impacto metabólico, con algunos estudios incluso sugiriendo el potencial de algunos de estos fármacos para contribuir a la pérdida ponderal.(50)

En cuanto a los antidepresivos, éstos son de los fármacos con menor impacto metabólico descrito entre toda la gama de tratamientos utilizados en el TB. Aun así, también entre este grupo se pueden encontrar diferencias importantes, por ejemplo con mirtazapina o paroxetina asociándose con más aumento de peso, o los antidepresivos duales como venlafaxina con mayor tendencia a aumentos de tensión arterial.(90)

No obstante lo comentado anteriormente, también se describe en varios estudios una tendencia a vulnerabilidad aumentada a problemas en metabolismo de glucosa incluso en pacientes “*drug naïve*” o en ausencia de tratamiento farmacológico,(53) lo que podría indicar ya una predisposición de base a estos problemas, independiente del tratamiento farmacológico, asociado a la patología en concreto, que se exacerbaría ante la toma de esta medicación.

Psiquiatría nutricional y del estilo de vida

La psiquiatría nutricional y la psiquiatría del estilo de vida estudian la relación de estos factores con la salud y la enfermedad, desarrollan intervenciones nutricionales o de estilo de vida para problemas de salud mental y evalúan la evidencia de estas intervenciones. En los últimos años están surgiendo enfoques de psiquiatría nutricional y psiquiatría del estilo de vida, y cada vez hay más evidencia de la utilidad de estos enfoques de forma complementaria, en conjunto con terapias habituales como el tratamiento farmacológico o la psicoterapia, con un impacto global positivo, con la posibilidad de mejorar la salud mental, la salud física y conducir a una mejora global de la funcionalidad.(132)

Psiquiatría nutricional

El campo de la psiquiatría nutricional investiga la calidad de la dieta como un factor modificable para enfermedades mentales. Cada vez existen más estudios que encuentran una asociación inversa entre dietas más saludables y menor riesgo de problemas mentales en general.(132,133) Los factores relacionados con la nutrición, como los patrones dietéticos y

los nutrientes específicos, pueden actuar como factores de riesgo al influir en las vías implicadas en la fisiopatología de los trastornos neuropsiquiátricos. Entre éstos, los mecanismos más destacados, potencialmente modulados por la dieta, son la inflamación o neuroinflamación, el estrés oxidativo, la plasticidad cerebral, el eje microbiota-intestino-cerebro, el eje hipotálamo-pituitaria-adrenal, la vía metabólica triptófano-quinurenina, la epigenética y la disfunción mitocondrial.(133,134) Otro de los objetos de estudio de la psiquiatría nutricional es el estudio y diseño de intervenciones dietéticas o con suplementos nutricionales, también llamados nutracéuticos, con el potencial de influir positivamente en los mecanismos anteriormente referidos, como enfoque complementario para prevenir y tratar los trastornos neuropsiquiátricos.(133,135)

En este ámbito también las herramientas estadísticas utilizadas tienen sus especificidades, como la utilización del análisis factorial, para poder examinar patrones dietéticos más que alimentos o nutrientes individuales, con los primeros estudios examinando patrones dietéticos y salud siendo publicados hace más de 40 años.(107) En cuanto a escalas utilizadas, lo más frecuente es utilizar cuestionarios de frecuencia alimentaria,(136) o de adherencia a dieta mediterránea,(102) aunque se empiezan a proponer escalas que evalúan el índice inflamatorio de la dieta.(137)

Psiquiatría del estilo de vida

En las últimas décadas, la medicina del estilo de vida surgió como una rama de la medicina basada en la evidencia, cuyo objetivo es mantener una salud óptima y prevenir, tratar y revertir las enfermedades crónicas, incluidos los trastornos de salud mental, a través de estrategias dirigidas a cambiar conductas no saludables y optimizar los pilares principales de la medicina del estilo de vida como la nutrición, la higiene del sueño, el manejo del estrés, la conexión social, la salud sexual y la fertilidad, la actividad física y minimizar el consumo de sustancias y las exposiciones ambientales.(138) También se abordan las vías neurobiológicas potencialmente compartidas entre múltiples factores del estilo de vida, simultáneas con las discutidas en el punto previo.(139)

Así, la psiquiatría del estilo de vida no deja de ser un sub apartado de esta disciplina, más orientado a las enfermedades mentales, como se ha visto en estudios recientes, con resultados positivos en diferentes patologías.(119) En consecuencia, la mejora de la salud física, el estado metabólico y los patrones de estilo de vida en el TB deberían ser los objetivos del enfoque terapéutico complementario no farmacológico, mejorando también la sintomatología psiquiátrica central, principalmente los síntomas depresivos y subdepresivos, y mejorando el funcionamiento y la calidad de vida de esta población.

Algunas de las limitaciones de esta área de estudio que durante años han limitado su desarrollo son la dificultad de obtener medidas objetivas de varios de los factores de estilo de vida, o la dificultad en obtener financiación para estudios de intervención. En este sentido, recientemente se están desarrollando escalas que ayuden a una evaluación más global de algunos de los principales factores de estilo de vida considerados.(139)

Microbiota

El eje microbiota-intestino-cerebro es una de las principales y más estudiadas vías implicadas en la interacción entre dieta y otros factores de estilo de vida, con la salud mental. Este eje interviene en la regulación de las funciones del sistema nervioso central, la conducta, el estado de ánimo y la ansiedad y, por tanto, tiene una implicación importante en la patogénesis de los trastornos neuropsiquiátricos.

Tanto conocer la composición como comprender si hay patrones específicos de cada enfermedad mental, o qué cambios en la microbiota pueden ser favorables o desfavorables, es crucial. Varios aspectos cotidianos, como nuevos patrones dietéticos, la utilización de antibióticos o el estrés continuo, pueden alterar la concentración y composición de la microbiota, conduciendo a un estado de disbiosis. Entender estas alteraciones es decisivo ya que se plantea la regulación de la microbiota como una posible herramienta terapéutica en el futuro, complementaria al tratamiento habitual con psicofármacos y psicoterapia.(15)

Se conoce que la disbiosis intestinal, a través de neurotransmisores producidos por microorganismos patógenos o a través del nervio vago, puede inducir activación de procesos neuroinflamatorios, estrés oxidativo, así como conducir a otros mecanismos

neuromoduladores y de regulación epigenética. El TB ya se había asociado con alteraciones en el sistema inmune pero se desconocía la causa, y la disbiosis se presenta como un posible intermediador.(15)

Se han descrito alteraciones de microbiota con un patrón transdiagnóstico, con reducción de ciertas bacterias antiinflamatorias, productoras de butirato, y un aumento de bacterias proinflamatorias en pacientes con depresión, trastorno bipolar, esquizofrenia y ansiedad.(140–142) La baja α -diversidad y la disbiosis con respecto a la abundancia de *Faecalibacterium* y *Bacteroides* podrían caracterizar el TB.(17) La disminución de la riqueza y la producción de butirato también fomentaría la inflamación, que puede ser una parte hasta ahora poco reconocida de la fisiopatología subyacente al TB.(17)

A nivel del TB hay ya diversos estudios que investigan el papel patogénico de la microbiota intestinal, la composición de la microbiota en pacientes con TB, en diferentes fases de la enfermedad como la eutimia, manía y depresión, las alteraciones de microbiota potencialmente causadas y finalmente el potencial terapéutico de alterar la composición de la microbiota en estos pacientes mediante diferentes intervenciones. (16,141) Así se abre una nueva línea de opciones terapéuticas en esta enfermedad como pueden ser: cambios dietéticos; la utilización de probióticos, microorganismos vivos que, cuando se ingieren en las cantidades adecuadas, pueden aportar beneficios para la salud de quien los consume (se pueden denominar psicobióticos las cepas con efectos positivos sobre la salud mental); prebióticos, compuestos que el organismo no puede digerir, pero que tienen un efecto fisiológico en el intestino al estimular, de manera selectiva, el crecimiento y la actividad de las bacterias beneficiosas; tratamientos antibióticos, como la minociclina o incluso trasplante fecal. (141) Se ha demostrado que la suplementación con probióticos no sólo alivia los problemas gastrointestinales, sino que también reduce la gravedad de los síntomas y las tasas de rehospitalización, y puede conllevar una mejora cognitiva. (143)

Psiconeuroimunoendocrinología

Considerando todo lo comentado, existen abordajes integrativos que debaten que, más que una base genética, el TB tiene una importante predisposición genética, modulada por varios

de los factores de estilo de vida ya mencionados. En este enfoque se considera que el estilo de vida occidental puede contribuir a la aparición y modificar la evolución del TB, ya que consideran que la inflamación y estrés crónico como dos mecanismos principales, impulsados por patrones alimentarios poco saludables, actividad física limitada y entornos sociales estresantes que a su vez pueden conllevar un mal funcionamiento del reloj interno. En este enfoque se propone que el tratamiento del TB debe centrarse en reducir el estrés y la inflamación mediante cambios en el estilo de vida, en lugar de simplemente aliviar temporalmente los síntomas con intervenciones psicofarmacológicas. (144)

Intervenciones nutricionales y sobre el estilo de vida en TB.

Teniendo en cuenta la importancia de la utilización de abordajes complementarios al tratamiento habitual, con intervenciones nutricionales y sobre el estilo de vida abordamos sucintamente la evidencia disponible en la actualidad. Se presentarán tanto abordajes dietéticos, de ejercicio, así como abordajes combinados sobre diferentes factores del estilo de vida.

Intervenciones dietéticas-nutricionales

En este tipo de abordajes se pueden considerar diferentes tipos de intervenciones, que incluyen cambios de patrón dietético, por ejemplo, como la utilización de dieta mediterránea, estudios en que se evalúan alimentos específicos, como pescado o frutos secos, estudios en que se examinan suplementos nutricionales con fines terapéuticos o intervenciones sobre la microbiota.

En relación a estudios de intervención con modificación de patrones dietéticos, dos de los más conocidos son el estudio SMILES (*Supporting the Modification of lifestyle in Lowered Emotional States*)(145) y el HELFIMED(146), en los cuales se ha demostrado como la aplicación de una intervención dietética a pacientes con depresión, tanto de forma individual como grupal respectivamente, mostraba mejoría de la clínica psiquiátrica, aunque también con mejoría en otros ámbitos como la calidad de vida percibida o menores gastos asociados en estudios de coste efectividad.(147) Un metaanálisis reciente que evalúa diferentes estudios que promueven la mejoría de patrones dietéticos en sintomatología ansiosa y

depresiva encuentra que la sintomatología depresiva se reduce de forma significativa con efectos menos marcados en la sintomatología ansiosa.(148) Recientemente también se está explorando la posibilidad de realizar intervenciones *online*, con el objetivo de mejorar la coste efectividad y poder alcanzar más gente.(149)

Pese a la literatura disponible sobre los potenciales efectos beneficiosos de la intervención dietética en el TB,(94,112) son escasos los estudios aleatorizados y controlados de intervención dietética específicos para pacientes con TB. En un estudio aleatorizado y controlado de intervención dietética en pacientes con TB, se encontró una reducción de la variabilidad emocional, energía e irritabilidad.(150) Existen estudios que engloban pacientes con TB dentro de un grupo más general de pacientes con trastorno mental severo, que sugieren un efecto beneficioso a nivel metabólico, de un programa de educación nutricional, previniendo el progreso del síndrome metabólico y protegiendo de eventos cardiovasculares.(151) Asimismo, la ingesta de marisco y alimentos ricos en omega 3 se ha asociado con efectos positivos en el TB.(112)

Se empieza también a debatir la utilidad de la dieta cetogénica en este grupo de pacientes, por su potencial de modulación de la función mitocondrial,(152,153) mientras que nuevos estudios proponen la utilización de intervenciones basadas en el ayuno intermitente por el impacto sobre los ritmos circadianos, especialmente alterados en pacientes con TB.(154)

Por otro lado, las intervenciones con suplementos nutricionales son un campo cada vez más estudiado, existiendo actualmente guías clínicas sobre recomendaciones de utilización de nutracéuticos (suplementos nutricionales con fines terapéuticos) o fitocéuticos (suplementos derivados de plantas con fines terapéuticos) en trastornos psiquiátricos.(155) Los nutracéuticos pueden actuar sobre vías neurobiológicas alteradas en el TB, como la inflamación, el estrés oxidativo y la disfunción mitocondrial, por lo que se discute su papel potencial como tratamientos complementarios para el TB.(156)

Los resultados más robustos disponibles hasta la fecha, en los diferentes estudios sobre suplementos nutricionales en TB, apoyan la utilización de ácidos grasos insaturados omega 3, con resultados prometedores para la utilización de coenzima Q10 y con efectos variables,

principalmente no significativos, de la suplementación con creatina, carnitina, vitamina D, inositol o N-acetilcisteína.(112,156) En las guías clínicas sobre utilización de nutracéuticos en trastornos psiquiátricos se considera que el omega-3 tiene un grado de recomendación débil mientras que la N-acetilcisteína no está de momento recomendada en el TB, encontrándose las recomendaciones más robustas con diferentes suplementos, para el tratamiento de la depresión unipolar.(155) En pacientes de edad avanzada con TB se recomienda ser particularmente cuidadoso con el cribado de posibles déficits nutricionales, como vitamina B12, vitamina D y folato, prevalentes en esta población, dado su impacto en la clínica afectiva, y que podrían requerir suplementación.(157) En relación a fitocéuticos, algo a tener en cuenta es la contraindicación de utilizar la hierba de San Juan por su riesgo de viraje maníaco.(155)

Finalmente, la modulación de la microbiota es una área de creciente interés, y cada vez se disponen de más estudios sobre su potencial utilización en diferentes trastornos psiquiátricos.(158) A excepción del trastorno depresivo mayor unipolar, que reúne el mayor volumen de evidencia y donde los probióticos están incluidos en las guías clínicas y pautas de tratamiento con nutracéuticos y fitocéuticos,(155) la evidencia actual es escasa para respaldar las intervenciones con prebióticos, simbióticos y alimentos fermentados en el tratamiento de otros trastornos mentales.(158) No obstante hay resultados prometedores, a nivel psicopatológico como cognitivo, asociados con la utilización de probióticos en TB, especialmente en pacientes con niveles más altos de inflamación sistémica y estrés oxidativo.(112,158) Estos estudios también inciden en la importancia de los hábitos alimentarios en general, como posibles moduladores de microbiota, aparte de la mera utilización de suplementos probióticos.

Intervenciones de ejercicio

El efecto del ejercicio en el TB está siendo estudiado; su principal mecanismo de acción propuesto es a través del efecto positivo sobre la neurogénesis.(115) La realización de ejercicio en el TB se ha asociado a mejoría de componentes de salud física, síntomas depresivos, funcionamiento global y calidad de vida percibida, encontrándose relaciones entre ejercicio vigoroso y sintomatología maníaca, en estudios longitudinales.(114,159) Aunque se dispone de escasa evidencia sobre estudios de intervención específicos en

pacientes con TB, en un estudio controlado se ha demostrado mejoría de funcionamiento social y disminución de alexitimia,(160) existiendo en la actualidad algunos protocolos para programas de intervención en desarrollo, con el objetivo de evaluar efectos a nivel psicopatológico, de funcionalidad y neurocognitivos.(161,162)

Intervenciones conjuntas o sobre estilo de vida

Finalmente, un área emergente de estudio en este ámbito es el desarrollo de intervenciones sobre el estilo de vida, que abordan de forma conjunta tanto intervenciones sobre dieta, ejercicio como otros factores de estilo de vida. La evidencia disponible presenta resultados inconsistentes, aunque con una tendencia a la mejoría de ciertos parámetros, especialmente de salud física, aunque también se propone su potencial efecto positivo sobre síntomas depresivos, funcionamiento global y calidad de vida percibida.(86,96) Los programas propuestos pueden ser de diferentes tipos, presenciales, ya sea de forma individualizada o grupal, u *online*.(163)

Teniendo en cuenta lo expuesto anteriormente, planteamos este proyecto de tesis con el objetivo de caracterizar mejor el estado metabólico en nuestra población con TB, y algunos de sus modificadores, como son variables de estilo de vida y farmacológicas.

El primer paso es realizar un estudio observacional sobre los patrones de alimentación y su relación con la actividad física, el síndrome metabólico y la evolución de la enfermedad en una muestra representativa de pacientes con TB, en nuestra área de influencia, así como obtener datos sobre el impacto farmacológico en esta interrelación.

El segundo paso será estudiar la relación entre el tratamiento con litio, comúnmente utilizado en el TB y el aumento de peso. Evaluaremos cuantitativamente la asociación del tratamiento con litio y el aumento de peso, así como los posibles moderadores de esta asociación a través de un metaenfoque. Hasta donde conocemos, ésta será la primera revisión sistemática y metaanálisis que proporcione un análisis cuantitativo centrado en el aumento de peso con el litio.

Sobre la base de los resultados de estos estudios, podremos caracterizar mejor a esta población en términos de patrones de estilo de vida, estado metabólico e implicaciones en el curso clínico, y comprender el impacto del tratamiento farmacológico, especialmente con litio, a nivel metabólico. Se espera que esta información sea de utilidad clínica, pueda generar nuevas hipótesis de estudio o servir de base para el diseño y desarrollo de nuevos programas de intervención ajustados a las necesidades específicas de nuestra población en concreto.



Review article

Does metabolic syndrome or its component factors alter the course of bipolar disorder? A systematic review

Anna Giménez-Palomo^a, Susana Gomes-da-Costa^a, Seetal Dodd^{b,c,d}, Isabella Pachiarotti^a, Norma Verdolini^a, Eduard Vieta^a, Michael Berk^{b,c,d,e,*}

^a Barcelona Bipolar Disorders Program, Hospital Clinic, University of Barcelona, IDIBAPS, CIBERSAM, Barcelona, Catalunya, Spain

^b IMPACT Strategic Research Centre, School of Medicine, Deakin University, Geelong, VIC, Australia

^c Department of Psychiatry, The University of Melbourne, Parkville, VIC, Australia

^d Centre for Youth Mental Health, The University of Melbourne, Parkville, VIC, Australia

^e Florey Institute of Neuroscience and Mental Health, The University of Melbourne, Parkville, Australia

ARTICLE INFO

Keywords:

Bipolar disorder
mania
depression
treatment
outcome
prognosis
biomarkers
medical
comorbidity
metabolic syndrome
diabetes
obesity
dyslipidaemia

ABSTRACT

Metabolic syndrome (MetS) and its component factors, obesity, hypertension, dyslipidaemia and insulin resistance, have shown a bidirectional relationship with the prevalence and severity of bipolar disorder (BD).

A systematic search of electronic databases (Pubmed, PsycINFO, clinicaltrials.gov) was conducted to explore and integrate current evidence about the role of MetS and its component factors with clinical outcomes of BD.

Thirty-four articles met the inclusion criteria. Studies were grouped by the metabolic factors assessed, which included MetS, obesity and body mass index (BMI), dyslipidaemia, impaired glucose metabolism (IGM), diabetes mellitus and hypertension. They were then classified according to outcomes such as course of episodes, rapid cycling, suicidal behavior, treatment response, and global and cognitive functioning.

Although current evidence remains controversial in most aspects of clinical outcomes, metabolic risk factors could alter the course of BD, with worse global functioning, poorer treatment response and a chronic course of illness, as well as enhancing rapid cycling. Further research is needed to elucidate the role of each risk factor in the mentioned outcomes.

1. INTRODUCTION

Bipolar Disorder (BD) is a chronic major affective illness where mood alternates between depression, euthymia and mania or hypomania (Vieta et al., 2018). Individuals suffering from BD are at increased risk for somatic diseases compared to healthy controls. These include high rates of obesity, hypertension, dyslipidemia, type 2 diabetes mellitus (T2DM) and metabolic syndrome (MetS) (Calkin et al., 2013a; McIntyre et al., 2005).

MetS was defined in 1998 by a WHO diabetes research group as a number of interrelated physiological, biochemical, clinical and metabolic factors that directly increase the risk of cardiovascular disease, T2DM and all-cause mortality (Alberti and Zimmet, 1998). The recent IDF definition requires the presence of three or more of the following criteria: (i) waist circumference relative to population and country-specific definitions; (ii) HDL-C <40 mg/dL (<1.04 mmol/L) in

men and <50 mg/dL (<1.29 mmol/L) in women or on drug treatment for reduced HDL-C; (iii) triglycerides ≥150 mg/dL (≥1.7 mmol/L) or on drug treatment for elevated TG; (iv) ≥130 mmHg systolic or ≥85 mmHg diastolic pressure or on antihypertensive drug treatment in a patient with a history of hypertension, and (v) fasting glucose ≥100 mg/dL or on drug treatment for elevated glucose (Alberti et al., 2009).

Regarding comorbid metabolic risk factors, T2DM occurs up to three times as often among individuals with BD, as it does in the general population, obesity is also highly prevalent, and glucose and lipids are dysregulated at high rates (Charles et al., 2016a). Moreover, BD has shown to increase the odds of re-hospitalization for comorbid non-mental conditions, which often remain underdiagnosed and undertreated (Dickerson et al., 2016). Patients with BD show increased mortality principally as a consequence of these risk factors and comorbidities, and largely via cardiovascular disease (Staudt Hansen et al., 2019; Correll et al., 2017). Particularly, some studies have associated

* Corresponding author at: IMPACT Strategic Research Centre, School of Medicine, Deakin University, Geelong, VIC 3320, Australia.
E-mail address: michael.berk@barwonhealth.org.au (M. Berk).

<https://doi.org/10.1016/j.neubiorev.2021.11.026>

Received 15 June 2021; Received in revised form 15 November 2021; Accepted 16 November 2021

Available online 17 November 2021

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the presence of type 1 or 2 diabetes mellitus with a higher risk of mortality caused by physical comorbidities in patients with BD (Dickerson et al., 2016; Pan et al., 2016); (Schoepf and Heun, 2014); (Sylvia et al., 2015).

Some psychotropic medications may cause increased appetite and weight gain, leading to MetS (De Hert et al., 2009; Hayes et al., 2016), but evidence is also increasing for a medication-independent association (Charles et al., 2016b). In addition, lifestyle factors in patients with BD, such as a lack of regular physical activity and increased caloric and simple carbohydrate intake, may play an etiologic role in the higher prevalence of metabolic illnesses (Calkin et al., 2013b). However, even after accounting for the above factors, the higher incidence of cardiovascular risk factors like T2DM among patients with BD remains unexplained, especially in treatment-naïve patients (Charles et al., 2016b).

The exact relationship between metabolic risk factors and BD is complex and not well understood. BD has been associated with a chronic low-grade pro-inflammatory state (Soczyńska et al., 2011), and hypotheses point at underlying immune dysfunctions paired with a chronic inflammatory state as risk factors for developing both BD and MetS (Charles et al., 2016b). Current evidence suggests that individual components of MetS might also be involved not only in inflammation and oxidative stress but also in micro and macro-cerebrovascular alterations leading to structural and functional abnormalities in the brain, which might have a negative effect on cognition in BD (Bora et al., 2019).

An association between MetS and changes in brain imaging has been found, including reduced thickness in frontal and temporal lobes in obese/overweight patients, widespread abnormalities in white matter structure in obese, dyslipidemic and diabetic patients, and reduced frontoparietal and subcortical volumes in cases of impaired glucose metabolism (Bora et al., 2019). In early BD, increased body mass index (BMI) has been also significantly associated with decreased white matter and temporal lobe volumes (Mazza et al., 2017; Bond et al., 2011); (Bond et al., 2019). Clinically significant weight gain (CSWG) has also shown greater volume loss in the left orbitofrontal cortex, left cingulate gyrus and left middle temporal gyrus, being the last one a predictive factor for more days with depression in patients with BD (Bond et al., 2019). This mechanism might underlie the association between MetS and a more severe illness course in BD (Mazza et al., 2017; Bond et al., 2011; Bond et al., 2019; Islam et al., 2018).

Preliminary investigations suggest that obesity and MetS might negatively impact the course of illness in BD, entailing lower quality of life, a more complex disease and other adverse outcomes, such as an increased risk of rapid cycling, functional impairment, a higher risk of suicide and poor response to treatment (McIntyre et al., 2005). For that reason, physical comorbidity has been postulated as an important risk factor for psychiatric readmission and other unfavorable outcomes in BD (Sprah et al., 2017).

Particularly, the presence of obesity in patients with depression appears to be predominantly associated with a diagnosis of BD (Petri et al., 2017), and appears to negatively affect the course and long-term prognosis of BD (Lackner et al., 2016). Increased number of manic and depressive episodes throughout life, a difficult-to-treat index affective episode, high recurrence of affective episodes, depressive predominance, and a shorter period of time until relapse have been reported more frequently in obese than non-obese patients (Fagioli et al., 2003).

Since growing research points to the potential negative implications of MetS in clinical outcomes of BD, we systematically reviewed the existing literature on the impacts of metabolic factors on the frequency of affective episodes, hospitalizations, cognitive impairment, suicidal behavior, global functioning and other potential outcomes in BD.

2. METHODS

This review was conducted according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement

(Moher et al., 2009).

2.1. LITERATURE SEARCH

Articles were carefully searched on PubMed, PsycINFO and clinicaltrials.gov databases. The search included articles from any date to September 5th, 2019, cross-checking the obtained references. Two independent researchers (AG and SG) performed the systematic search. Full-texts were screened, if necessary, to establish the eligibility of articles. Discrepancies were resolved by a third researcher (SD).

For MEDLINE/Pubmed/Index Medicus, authors used the following search strategy: ((metabolic syndrome[Title/Abstract] OR metabolic disturbances[Title/Abstract] OR insulin resistance[Title/Abstract] OR fasting glycemia[Title/Abstract] OR glucose metabolism[Title/Abstract] OR glucose impaired metabolism[Title/Abstract] OR diabetes [Title/Abstract] OR cholesterol[Title/Abstract] OR blood pressure [Title/Abstract] OR hypertension[Title/Abstract] OR obesity[Title/Abstract] OR abdominal perimeter[Title/Abstract] OR abdominal fat [Title/Abstract] OR abdominal girth[Title/Abstract] OR waist circumference[Title/Abstract] OR triglycerides[Title/Abstract] OR hypertriglyceridemia[Title/Abstract] OR microalbuminuria[Title/Abstract] OR urine albumin[Title/Abstract]) AND ((bipolar disorder[Title/Abstract] OR bipolar affective[Title/Abstract] OR manic[Title/Abstract] OR mania[Title/Abstract] OR bipolar depression[Title/Abstract] OR hypomania[Title/Abstract] OR hypomanic[Title/Abstract])) AND ((outcome OR outcomes OR worsening OR worsens OR improvement OR improves OR course OR prognosis OR prognostic OR cycling OR recurrence OR recurrences OR hospitalization OR hospitalizations OR hospitalized OR hospitalisation OR hospitalisations OR hospitalised OR admission OR admissions OR admitted)). This produced 953 records. For PsycINFO the same search strategy was employed, specifying (bipolar disorder OR bipolar affective OR manic OR mania OR bipolar depression OR hypomania OR hypomanic) to be present in the title; the search yielded 281 records, showing additional records to the PubMed search. For the <https://clinicaltrials.gov/> database, keywords were: metabolic syndrome AND bipolar disorder, and produced 27 records.

Three additional articles were identified from a hand search of reference lists and were included in the pool of records identified by and selected from PubMed, PsycINFO and clinicaltrials.gov.

2.2. STUDY SELECTION

Longitudinal studies on the effect of metabolic disturbances in the course or prognosis of BD were included. Studies including adults or children and adolescents were all considered. Studies could be experimental (randomized clinical trials (RCT), quasi-RCTs, non-RCTs), quasi-experimental (controlled before and after studies, interrupted time series), and observational (cohort, case-control, registry studies). We excluded animal and cell cultures studies, studies resulting from databases that did not directly relate metabolic risk factors with BD outcomes, and studies focusing on the effects of pharmacological treatments. Also excluded were studies on the effects of metabolic disturbances that did not report results of each risk factor separately (apart from those evaluating patients with MetS) and studies assessing the course of mental disorders without separating the BD group from other mental illnesses. Meta-analyses and reviews were used as evidence to support information that could not be drawn from individual studies. Open studies, case reports or series, letters to the editor, author responses to criticisms, opinion papers, editorials, surveys, studies focusing only on biomarkers such as genetic investigations and brain imaging, were excluded.

For this review, the PICO worksheet (Miller and Forrest, 2001), the AMSTAR form (Shea et al., 2017), and the PRISMA checklist (Moher et al., 2009) were completed. The strength of recommendations was assessed using the Australian National Health and Medical Research Council (NHMRC) levels of evidence and grades for recommendations

for developers of guidelines (Australian Government, 2009). Risk of bias was addressed according to the Cochrane Risk of Bias Tool (Higgins et al., 2011), classifying each study into a high, low or unclear category for the selection, reporting, performance, detection, attrition, and other dimensions, which rated the global quality of the paper.

3. RESULTS

The screening identified 1,264 records. From these records, 211 duplicates were found and 1,002 were excluded for the mentioned criteria by their title and abstract. Fifty-one articles were chosen for full-text screening. Since three papers extracted data from the same registry (Hajek et al., 2005; Hajek et al., 2008; Ruzickova et al., 2003), data assessing the same outcomes was analyzed from just one of them (Ruzickova et al., 2003); however, data assessing separate outcomes was analyzed from the corresponding publication. Thirty-six papers were finally selected for analysis (Fig. 1).

The studies included were mostly cross-sectional and heterogeneous in the outcomes measured. Twenty-one studies evaluated overweight or obesity, 11 impaired glucose metabolism, 6 MetS, 6 dyslipidemia and 3 hypertension. The studies investigated the relationship between metabolic risk factors with course of episodes ($n = 22$), suicidal behavior ($n = 13$), global functioning ($n = 10$), rapid cycling ($n = 4$), treatment response ($n = 4$) and cognitive functioning ($n = 4$). The details of each study are included in Table 1.

Most studies were of good to satisfactory quality of evidence, but none was excellent, despite most studies including large samples. Reasons varied, with high rate of attrition bias, not assessing confounding

variables, small sample sizes, and not including various metabolic disturbances in the same studies. Hence, the total strength of recommendations of this review according to the National Health and Medical Research Council (Australian Government, 2009) is from satisfactory to good. Below, we summarize the findings concerning the relationship between different metabolic risk factors and the course of illness in BD.

3.1. Metabolic syndrome

3.1.1. Course of episodes

A cross-sectional study showed that patients with both MetS and BD had significantly more previous hospitalizations compared to patients with BD alone ($p = 0.024$). Moreover, comorbid patients had a higher risk of mania as a first mood episode ($p = 0.033$) (Bai et al., 2016).

The presence of MetS has also been significantly associated with percentage of weeks in full-threshold pure depression ($p = 0.02$) and percentage of weeks receiving antidepressant medications ($p = 0.001$) in the preceding 6 months, but it not with manic symptoms (Li et al., 2019). No significant differences were found in terms of the scores on the Hamilton Depression Rating Scale (HDRS) and the Young Mania Rating Scale (YMRS) in a cross-sectional study assessing outpatients with BD (De Almeida et al., 2009).

Another study reported that individuals with BD and MetS showed a significant later age at first treatment for both phases ($p = 0.024$ for depression and $p = 0.035$ for mania) when compared with bipolar patients without MetS. There was a trend towards later age at onset of first manic episode ($p = 0.066$) for the group with MetS. Differences in number of hospitalizations or episodes for either depression or mania, in

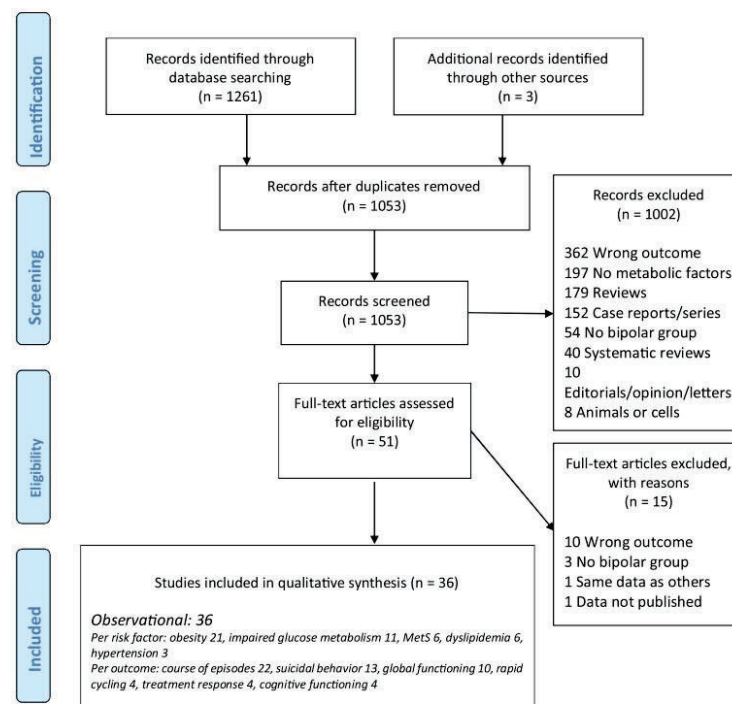


Fig. 1. PRISMA 2009 Flow Diagram; Search carried out on September 5th, 2019. Databases: PubMed → PsycINFO → ClinicalTrials.gov.

Table 1
Summary of included studies on metabolic disturbances and the course of illness in BD.

Studies by first author and date in reverse order	Sample size (N)	Study design	Metabolic factors assessed	Main outcomes	Quality (includes bias)
Steardo et al., 2019	91 BD	CS	IGM	- Compared to patients with normal glucose metabolism, BD patients with IGM showed worse response to mood stabilizers ($p < 0.002$).	3
Li et al., 2019	162 BD; adolescents and young adults	CS	MetS	- MetS was associated with percentage of weeks in full-threshold pure depression ($p = 0.02$) and percentage of weeks receiving antidepressants ($p = 0.001$).	3
Hu et al., 2017	110 BD, 57 HC	3 years	OB	- Increased BMI during follow-up was associated with an increased risk of recurrence to any mood episode ($p = 0.02$).	3
Buoli et al., 2017	238 BD	CS	OB	- RC subjects had more often OB ($p < 0.05$) and had a trend to hypercholesterolemia ($p = 0.08$) than non-RC individuals.	3
Shapiro et al., 2017	75 BD, 47 HC; adolescents	CS	OB	- Obese patients were found to have more commonly history of suicide attempt ($p = 0.001$).	3
Mora et al., 2017	52 BD, 69 HC	CS; 6 years	OB	- OB was significantly associated with cognitive impairment in euthymic BD ($p = 0.018$), and it also appeared to affect cognition in the long term ($p = 0.033$).	3
Bond et al., 2017	80 BD, 46 HC; adolescents and young adults	12 months	OB	- Neither baseline BMI nor BMI change predicted lower cognitive functioning.	3
Goldstein et al., 2016	295 BD, 1,112 UD, 8,716 HC; adolescents	CS	OW, OB	- OW and OB in adolescents with BD were associated with significantly higher lifetime rates of suicide attempt ($p = 0.05$). - OW and OB were also related with being hospitalized overnight for depression ($p = 0.05$), and receiving general medical treatment ($p = 0.05$).	3
Bai et al., 2016	143 BD	CS	MetS	- Patients with MetS had significantly more previous hospitalizations ($p = 0.024$), more first mood episodes with mania ($p = 0.033$), poorer global functioning (GAF; $p = 0.035$), poorer insight (SAI; $p = 0.027$), and more impaired executive function (conceptual level response on the WCST; $p = 0.007$) than those without MetS. - Patients with OB showed significantly less improvement in global illness severity ($p = 0.01$), depressive and total mood symptoms ($p = 0.005$ and $p = 0.007$ respectively), suicidality ($p = 0.001$), functioning ($p = 0.021$), and a trend to worse overall life satisfaction ($p = 0.053$) compared to non-obese subjects. - There were bigger differences in improvement between obese and non-obese patients in the last three months of the trial.	3
McElroy et al., 2016	482 BD	6 months	OB	- Adominal obesity predicted less improvement on overall severity ($p = 0.08$), depression ($p = 0.024$), suicidality ($p = 0.019$), functioning ($p = 0.032$), and life satisfaction ($p = 0.008$), but not in total mood symptomatology. - Increased baseline BMI predicted significantly less improvement in global illness severity ($p = 0.018$), suicidality ($p = 0.002$), and overall life satisfaction ($p = 0.022$), but not in depression, total mood symptomatology nor functioning. - MetS had no effect on outcome (data not shown). - Higher BMI was non-significantly associated with longer time until recovery ($p = 0.06$). - BMI acted as a moderator of recovery status after controlling for age, sex, number of episodes ($p = 0.04$), number of depressive episodes ($p = 0.03$) and affective instability ($p = 0.02$). Its moderating effects were reduced to a statistical trend after adjusting for illness duration, and reduced to non-significance after controlling for lifetime anxiety, number of anxiety disorders and sleep type. - BMI did not moderate the effects of treatment condition on time to recovery.	3
Peters et al., 2016	199 BD	CS	OB	- Individuals with IGM had longer illness duration ($p = 0.007$) and a higher number of previous manic/hypomanic episodes ($p = 0.028$) than those without IGM. - A moderating effect of IGM was observed on the association between number of mood episodes and frequency of episodes, being greater in the IGM subgroup ($p = 0.029$).	3
Mansur et al., 2016	55 BD	CS	IGM	- There was a negative correlation between lifetime mood episodes and persistence of depressive symptoms in the euglycemic group, but a positive one in the IGM participants. - A positive history of suicide attempts was associated with lifetime mood episodes in the euglycemic patients, but not in the IGM subgroup. - Interactions between lifetime mood episodes and IGM on age at onset ($p = 0.037$), illness duration ($p = 0.030$) and episode frequency ($p = 0.026$) were statistically significant after removing outliers, whereas on history of suicide attempts and HDRS total score were not.	3
Leopold et al., 2016	85 BD	CS	IGM	- Global functioning was significantly lower in the group with IGM compared to the controls ($p = 0.015$). - Quality of life was significant lower in the group with IGM ($p = 0.001$).	3

(continued on next page)

Table 1 (continued)

Studies by first author and date in reverse order	Sample size (N)	Study design	Metabolic factors assessed	Main outcomes	Quality (includes bias)
				- There was a trend for lower quality of life in the mental and physical component summary scale of the SF-12, which were non-significant. - Polarity at onset, age at onset, BD diagnostic subcategories, number of lifetime episodes, history of long-term disability, suicidal behavior, and family or personal history of psychosis were not associated to IGM. - Chronic course of BD was significantly related to IGM ($p = 0.031$). - IR or T2DM remained strong predictors of an unfavorable course, even after controlling for BMI, but not BMI ($p < 0.001$). - Patients with T2DM or IR had higher rates of RC than euglycemic patients (38.5%–39.5% vs. 18.2%; $p = 0.012$). - Glucose metabolic status was related to lithium response (3.2% of non-response in euglycaemic patients vs. 36.7%–36.8% in IR and T2DM patients; $p = 0.035$). A greater proportion of euglycaemic patients achieved remission with lithium compared to IGM patients ($p < 0.0001$). - Response to lithium was also negatively associated with a continuous measure of IR ($p = 0.013$). - A significant difference was seen between individuals with BD with a history of WCYC to non-WCYC in the number of depressive episodes ($p = 0.03$) and manic episodes ($p = 0.013$). - People with WCYC showed significantly more lifetime depressive and manic episodes (multivariate result: $p = 0.46$). - There were no differences concerning suicide attempts and staging. - There are no different concentrations of total cholesterol, LDL, HDL, TG, and total lipids between unipolar and bipolar depressed patients showing suicidal behaviors during the 3 months before admission. - OW and OB were not associated to illness progression. - Patients with BD and higher BMI scored worse on nonverbal memory ($p = 0.05$), but not on other cognitive domains. - Obese subjects were significantly more likely to have a major depressive episode in the next 3 years ($p = 0.03$), and also to receive counseling/psychotherapy for depression ($p = 0.04$), compared to non-obese subjects, but these differences were no significant after controlling for demographic variables. - Lifetime suicide was significantly more prevalent among obese (29.78%) versus non-obese (20.90%; $p = 0.03$) subjects. - No significant differences were found in new episodes of mania/hypomania. - Obese subjects demonstrated greater reductions in the general health subscale of the SF-12, but not other subscales. - Obese BD subjects reported greater duration of lifetime longest major depressive episodes ($p = 0.001$), higher lifetime prevalence of anxiety disorders, and lower past-year prevalence of SUD. - Obese BD subjects were more likely to receive medications for depression ($p < 0.001$), to seek treatment from a professional ($p = 0.003$), to be hospitalized ($p = 0.004$) and to attend the emergency department ($p < 0.001$) for depression. - Worse functioning on all but one SF-12 subscales was seen in obese BD patients ($p < 0.05$). - Hypertension and OB were associated with higher rates of outpatient service use in patients with BD ($p < 0.05$), but not T2DM or dyslipidemia. - Hypertension and OB did not increase service use over time or time to recovery for BD. - Significant interactions were present for dyslipidemia and OB in the reported reduction of acute service use after diagnosis of BD ($p < 0.05$), but they did not change the overall course of reductions in acute service over time. - An inverse linear effect of cholesterol on manic symptom burden at the follow-up was observed ($p = 0.01$). - Bipolar individuals with MetS had a later age at first treatment for both phases compared with non-MetS individuals ($p = 0.024$ for depression and $p = 0.035$ for mania). - There was a trend towards later age at onset of first manic episode ($p = 0.066$) in patients with MetS. - Individuals with MetS had a greater number of psychiatric hospitalizations overall ($p = 0.022$). - No differences between groups were found in the percentage of individuals who attempted suicide, the number of suicide attempts, age at onset of first depressive episode, number of lifetime depressive or manic episodes, or in the rates of psychiatric comorbidity. - No significant differences were found in the amount of days with mood symptoms between patients with normal weight, OW/OB and subjects with CSWG. - No significant differences were found in the relapse rates between these groups.	
Calkin et al., 2015	121 BD	CS	IGM, OB		3
Reininghaus et al., 2014	101 BD; 48 HC	CS	OB		3
Ainiyet et al., 2014	52 BD, 171 UD	CS	HDL, LDL, TG		3
Post et al., 2014	634 BD	CS	OW, OB		3
Silveira et al., 2014	65 BD, 37 HC	CS	OW, OB		3
Goldstein et al., 2013	1,600 BD	CS; 3 years	OB		3
Goldstein et al., 2011	43,093 participants (1,905 BD)	CS	OW, OB		3
Jerrell et al., 2010	979 BD children, 862 BD adolescents; 4,500 HC	9 years	OB, IGM, BP, Total cholesterol		3
Fiedorowicz et al., 2010	65 BD; 66 other mental illnesses	CS; 20–25 years	Total cholesterol		3
McIntyre et al., 2010	99 BD	CS	MetS		3
Bond et al., 2010	46 BD	CS; 12 months	OW, OB, CSWG		3

(continued on next page)

Table 1 (continued)

Studies by first author and date in reverse order	Sample size (N)	Study design	Metabolic factors assessed	Main outcomes	Quality (includes bias)
				- No significant differences were found in mean 12-month YMRS, MADRS, and HDRS scores between patients with and without baseline and 12-months OW/OB and those with or without CSWG. - No differences in the proportion of patients with impaired functioning were found between normal weight and OW/OB patients. - CSWG was associated with impaired functioning over the previous 6 months, but over the previous 12 months it was only significant in females ($p = 0.020$).	
De Almeida et al., 2009	84 BD	CS	MetS, OB	- Neither patients with MetS nor those with OB had different lifetime history of suicide attempts or scores on the scales employed (HDRS, YMRS and CGI) than those without MetS or OB. - Average total cholesterol was statistically significantly lower ($p = 0.013$) among suicide attempters than among suicide non-attempters	3
Vuksan-Cusa et al., 2009	40 BD (males)	CS	MetS, LDL, HDL	- Suicide attempters had statistically significantly lower TG levels than non-attempters ($p = 0.028$). - No significant differences were seen between patients with or without history of lifetime suicide attempts in HDL, LDL, BP and blood glucose levels. - Duration of illness resulted to be correlated with BMI ($p = 0.02$). - Patients with a history of RC showed a trend toward higher BMI, but that was not statistically significant.	3
Calkin et al., 2009	276 BD	CS	OB	- There was no significant difference in BMI between subjects with and without a history of psychotic episodes and with or without suicidal behavior. - Patients with complete remission on lithium had a significantly lower BMI compared to those who showed partial or no therapeutic benefit ($p = 0.01$).	3
Hajek et al., 2008	252 BD	CS	IGM	- Worse GAF scores were correlated with higher BMI ($p < 0.05$).	3
Hung et al., 2007	14 RD, 21 UD, 15 BD (males)	CS	IGM	- A statistically significant association was found between lifetime history of RC and diagnosis of T2DM ($p = 0.04$). - Insulin sensitivity was negatively correlated with severity of depressive symptoms ($p = 0.04$).	3-4
Chung et al., 2007	82 BD	CS	Total cholesterol, TG	- Serum cholesterol levels did not show differences between patients with or without prior depressive episodes. - The severity of mania or depression was not significantly related to serum cholesterol or TG levels. - Serum TG levels were found to have a significantly negative correlation with BPRS scores ($p = 0.031$).	3
Fagioli et al., 2005	171 BD	CS	MetS, abdominal OB	- MetS was not associated to a different CGI score or GAF score. - Suicide attempts were more frequent in patients with MetS (53%) than in patients without MetS (36%; $p = 0.05$).	3
Hajek et al., 2005	252 BD	CS	IGM, OW, OB, BP	- Abdominal OB was related to a history of suicide attempts ($p = 0.04$). - Significant low GAF scores were found in patients with BD in clinical remission with versus without T2DM ($p = 0.04$). - GAF scores of patients with hypertension or OW/OB did not differ from those without these characteristics.	3
Fagioli et al., 2003	175 BD	9 years	OB	- Risk of recurrence was higher in the obese group than in the non-obese group ($p < 0.04$), being depressive recurrences significantly higher ($p < 0.02$). - There were no statistically significant differences in number of manic or mixed recurrence episodes. - Obese patients had a significant shorter time to recurrence than non-obese patients ($p < 0.02$).	3
Ruzickova et al., 2003	222 BD	CS	IGM	- Diabetic patients had significant higher rates of RC ($p = 0.02$) and chronic course of BD ($p = 0.006$), scored lower on the GAF scale ($p = 0.01$) and were more often on disability for BD ($p < 0.001$).	3
Tsai et al., 2002	82 BD	CS	IGM, total cholesterol	- There were no significant differences between suicide completers and controls in levels of fasting blood sugar and serum cholesterol on the index hospitalization.	3
Cassidy et al., 1999	345 BD	CS	IGM	- Inpatients with comorbid T2DM had significantly more lifetime psychiatric hospitalizations than the non-diabetic subjects ($p < 0.05$).	3

Abbreviations: BD, bipolar disorder; CS, cross-sectional; IGM, impaired glucose metabolism; OR, odds ratio; CI, confidence interval; MetS, metabolic syndrome; HC, healthy controls; OB, obesity; HR, hazard ratio; BMI, body mass index; RC, rapid cycling; UD, unipolar depression; OW, overweight; IR, insulin resistance; T2DM, type-2 diabetes mellitus; GAF, Global Assessment of Functioning Scale; SAI, Schedule for the Assessment of Insight; WCST, Wisconsin Card Sorting Test; RCT, randomized clinical trial; SF-12, 12-Item Short Form Health Survey; WCYC, weight cycling; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; TG, triglycerides; SUD, substance use disorder; CSWG, clinically significant weight gain; YMRS, Young Mania Rating Scale; MADRS, Montgomery-Asberg Depression Rating Scale; HAM-D, Hamilton Depression Rating Scale; CGI, Clinical Global Impression Scale; BP, blood pressure; RD, reactive depression; BPRS, Brief Psychiatric Rating Scale. Quality assessment: 1, first rate evidence; 2, good evidence; 3, fair evidence; 4, poor evidence.

the age of onset of first depressive episode or in the rates of psychiatric comorbidity were not seen. However, individuals with MetS had a significant greater number of psychiatric hospitalizations overall ($p = 0.022$) (McIntyre et al., 2010).

3.1.2. Suicidal behavior

The percentage of patients reporting a history of at least one suicide attempt was higher in patients with MetS (53%) than in patients without MetS (36%; $p = 0.05$) (Fagioli et al., 2005).

Other authors reported no statistically significant differences in terms of the lifetime history of suicide attempts, neither in the percentage of individuals who attempted suicide nor in the number of suicide attempts (De Almeida et al., 2009; McIntyre et al., 2010).

3.1.3. Global functioning

In a study about the prevalence and predictors of MetS in adolescents with BD in the 6 months preceding the assessment of MetS, with global functioning measured using the Children's Global Assessment Scale (CGAS), only a non-significant association between lower lifetime global functioning at intake and presence of MetS was found (Li et al., 2019). Two independent cross-sectional studies did not find statistically significant differences between patients with and without MetS, neither for Clinical Global Impression (CGI) Severity scale score nor for GAF score (De Almeida et al., 2009; Fagioli et al., 2005).

However, another study found that patients with BD and MetS had significantly poorer global functioning measured with the Global Assessment of Functioning (GAF) scale ($p = 0.035$), poorer insight according to the Schedule for the Assessment of Insight (SAI) ($p = 0.027$), and more impaired executive function determined with the Wisconsin Card Sorting Test (WCST) ($p = 0.007$) than patients without MetS (Bai et al., 2016).

3.2. Body mass index and obesity

3.2.1. Course of episodes

A prospective cohort study that investigated BMI changes in patients with BD showed that increased BMI during a 3-years follow-up period was associated with an increased risk of recurrence of any mood episode ($p = 0.02$), but there was no statistical association between baseline BMI and recurrence (Hu et al., 2017). A similarly designed study examining the association between obesity at a first assessment and the subsequent course of BD within 3 years of follow-up showed that obese subjects were significantly more likely to have a major depressive episode during follow-up ($p = 0.03$), and also to receive counseling or psychotherapy for depression ($p = 0.04$), compared to non-obese subjects. However, these differences were no longer significant after controlling for baseline demographic variables. No significant differences in new episodes or treatment of mania/hypomania were observed in this study (Goldstein et al., 2013). Other authors assessing the course of illness over 12 months showed no statistically significant differences in relapse rates between patients with and without baseline overweight or obesity or patients with and without CSWG (Bond et al., 2010). No significant differences were detected in mean Montgomery-Asberg Depression Rating Scale (MADRS), YMRS and HDRS scores between all groups (De Almeida et al., 2009; Bond et al., 2010).

Nevertheless, an observational study aiming to identify obesity at baseline as a possible predictor for recurrence in BD showed that the percentage experiencing depressive recurrences in 2 years was significantly greater in the obese group than in the non-obese group (32.6% versus 13.9%; $p < 0.02$). However, the difference in number of manic or mixed recurrence episodes between the obese and the non-obese groups was not statistically significant (Fagioli et al., 2003). A Kaplan-Meier survival analysis confirmed that the time to recurrence for patients who were obese at baseline was significantly shorter than that of patients who were not obese at baseline, being time to depressive recurrence significantly shorter in the obese group (Fagioli et al., 2003).

Other research showed that obesity was associated with higher rates of outpatient service use in patients with BD ($p < 0.05$). However, obesity did not increase service use over time or time to recovery for BD. Prior to the diagnosis and treatment of BD, there were higher rates of outpatient service use, and obesity interacted significantly in the reported reduction of acute service use after the diagnosis of BD ($p < 0.05$) (Jerrell et al., 2010).

Another study retrospectively assessed weight cycling, defined as repeated periods of weight loss and gain. This showed a significant difference between individuals with BD with a history of weight cycling compared to non-weight cycling subjects in a higher number of affective episodes ($p = 0.03$ for depressive and $p = 0.013$ for manic episodes) and illness duration (multivariate result: $p = 0.46$) (Reininghaus et al., 2014).

Regarding duration of mood episodes, a greater duration of lifetime longest major depressive episodes in obese patients has been reported ($p = 0.001$) (Goldstein et al., 2011). Increased baseline BMI was seen to predict significantly less improvement in global illness severity ($p = 0.01$), but not less improvement in depression or in total mood symptomatology. Nevertheless, participants with abdominal obesity improved significantly less on measures of overall severity ($p = 0.08$) and depression ($p = 0.024$), compared to patients without abdominal obesity, but not in total mood symptomatology (McElroy et al., 2016).

In contrast, other studies found that a higher BMI at baseline or after a follow-up period was not a significant independent contributor to illness progression compared to patients who were not overweight (Bond et al., 2010; Post et al., 2014; Calkin et al., 2015) and it did not predict likelihood of recovery. Patients who experienced CSWG at 12 months were suggested to have more days with depression and any mood symptoms than patients without CSWG, and fewer days with mania, but these differences were also not significant (Bond et al., 2010). BMI was found to be a significant moderator of recovery status after controlling for age, sex, number of manic and depressive episodes ($p = 0.04$) and affective instability ($p = 0.02$), but the moderating effects of BMI were reduced to a statistical trend ($p = 0.06$) after adjusting for illness duration (Peters et al., 2016).

Overweight and obese BD subjects were significantly more likely to receive medications for depression ($p < 0.001$), to be hospitalized for depression ($p = 0.05$, $p = 0.004$), and to attend the emergency department due to depression ($p < 0.001$) (Goldstein et al., 2011; Goldstein et al., 2016).

3.2.2. Rapid cycling

Regarding the frequency of relapses, a study comparing socio-demographic and clinical variables in rapid cycling versus non-rapid cycling bipolar patients showed through a logistic regression that the first group of patients had obesity over two times as frequently before the onset of rapid cycling (21.4% vs. 7.6%; $p = 0.03$). The last pharmacological treatment was assessed and compared between groups (rapid cycling vs non-rapid cycling), not differing significantly, excepting with asenapine, which was more frequently prescribed in rapid cycling patients ($p < 0.05$). This suggests that obesity could be a possible predictor of rapid cycling in BD (Buoli et al., 2017).

However, according to a previous study that also found a statistically significant difference, this was no longer significant when both insulin resistance/T2DM and BMI were entered into a logistic regression to control for present and lifetime use of antipsychotic medication (Calkin et al., 2015). A trend toward higher BMI was seen in another sample including patients with history of rapid cycling compared to those without, but the result was not statistically significant (Calkin et al., 2009).

3.2.3. Suicidal behavior

Evidence about the relationship between lifetime suicide attempts and higher BMI remain controversial. Statistically significant higher rates of suicide attempt among obese versus non-obese adolescent and

adult subjects have been reported in some studies ($p = 0.05$, $p = 0.05$, $p = 0.03$, $p = 0.001$) (Fagioli et al., 2005; Goldstein et al., 2013; Goldstein et al., 2016; Shapiro et al., 2017). Increased baseline BMI ($p = 0.001$) as well as abdominal obesity ($p = 0.019$) predicted significantly less improvement in suicidality after six months of treatment (McElroy et al., 2016).

Nevertheless, in a cross-sectional study obese compared to non-obese patients did not show a statistically significant higher number of suicide attempts (De Almeida et al., 2009) or different Suicide Assessment Scale (SUAS) scores (De Almeida et al., 2009). A paper concerning lifetime suicide attempts between patients with and without weight cycling did not find significant differences (Reininghaus et al., 2014).

3.2.4. Treatment response

In a study reporting the relationship between BMI at baseline and lithium response, patients who achieved complete remission of psychiatric symptoms on lithium had a significantly lower BMI compared to those who showed partial or no therapeutic benefit ($p = 0.01$), although this was not adjusted by number of previous episodes. These patients had a mean BMI in the healthy weight range. Patients who had a partial response to lithium had a mean BMI in the overweight range, while those showing no response to lithium had a mean BMI in the obese range (Calkin et al., 2009).

3.2.5. Cognitive functioning

The presence of obesity in subjects with BD has been often related to cognitive functioning, associating obesity with worse cognitive performance, mainly in executive functioning compared to non-obese bipolar subjects ($p = 0.018$), and with cognitive dysfunction maintained over time ($p = 0.033$) (Calkin et al., 2009; Mora et al., 2017). A trend towards a negative correlation between the BMI and the cognitive domain of nonverbal memory score was found in another study ($r = -0.246$, $p = 0.05$), but not for other cognitive domains (processing speed, attention, verbal memory, working memory or executive function) (Silveira et al., 2014).

However, other studies assessing adolescents and adults with BD found that neither baseline BMI nor BMI change predicted lower cognitive functioning (Hajek et al., 2005; Bond et al., 2017).

3.2.6. Global functioning

A study correlated worse global functioning, according to GAF scores, with higher BMI ($p < 0.05$) (Calkin et al., 2009), and another showed significantly worse functioning on the general health subscale of the Short Form Health Questionnaire-12 (SF-12) in obese patients, as compared to non-obese subjects (Goldstein et al., 2013; Goldstein et al., 2011). Other authors displayed that increased baseline BMI had a trend to predict worse overall life satisfaction ($p = 0.053$), but not less improvement in functioning, whereas abdominal obesity predicted significantly less improvement on measures of functioning ($p = 0.032$), and life satisfaction ($p = 0.008$) compared to patients without abdominal obesity (McElroy et al., 2016). One study found no significant differences in CGI scores between obese and non-obese participants (De Almeida et al., 2009).

Nevertheless, other authors demonstrated that overweight or obesity at baseline and 12-month were not associated with impaired functioning in a study that used the Multidimensional Scale of Independent Functioning (MSIF) global functioning score, whether functioning was assessed over the previous 30 days or over the previous 6 months (Bond et al., 2010). However, patients with CSWG had significantly greater impairment in global functioning over the previous 30 days than those without CSWG. Over the previous 6 months, patients with CSWG had significant impairment in both global functioning and role functioning. The proportion of patients who were overweight or obese at baseline or 12-months and experienced moderate to severe impairment in 12-month global functioning was very similar to that of patients with normal weight. There were more patients with CSWG who experienced

moderate to severe impairment than patients without CSWG, but this difference did not reach statistical significance. When males and females were analyzed separately, CSWG was associated with impaired 12-month global functioning in females but not in males (Bond et al., 2010).

3.3. Dyslipidemia

Whilst most of the studies assessing lipid blood levels in individuals with BD have been conducted in inpatients, others assessed the clinical course of illness in outpatients during a follow-up.

3.3.1. Course of episodes

Some evidence reported that lipid tests in acute inpatients showed a non-significant trend ($p = 0.081$) to lower serum cholesterol levels in patients with prior depressive episodes than those of patients without prior depressive episodes. The symptomatic severity of mania (YMRS scores) did not demonstrate a significant correlation with serum cholesterol levels or triglyceride levels, whereas the symptomatic severity of depression (scored with the HDRS) trended towards a positive correlation with serum cholesterol levels, which was also non-significant ($p = 0.065$). Serum triglyceride levels were found to have a significantly negative correlation with Brief Psychiatric Rating Scale (BPRS) scores ($p = 0.031$), and two subscales of the BPRS (thinking disturbance, $p = 0.007$; hostile/suspiciousness, $p = 0.001$) (Chung et al., 2007).

In a prospective study where total cholesterol levels at baseline and depressive or manic symptom burden at follow-up (up to 25 years) were assessed, there was no effect on depressive symptom burden. A statistically significant, inverse linear effect of cholesterol on manic symptom burden was observed ($p = 0.01$), controlling for age, gender, and use of a mood stabilizer in the regression model (Fiedorowicz et al., 2010).

Other evidence showed no association between dyslipidemia and higher rates of outpatient service use (Jerrell et al., 2010). In a study that showed a reduction of acute service use after the diagnosis of BD, dyslipidemia interacted significantly with this reduction ($p < 0.05$), but it did not change the overall course of acute service use over time (Jerrell et al., 2010).

3.3.2. Rapid cycling

A study enrolling patients from different community mental health centers revealed a statistically significant relationship between hypercholesterolemia and higher rates of rapid cycling in bipolar patients ($p < 0.05$) (Buoli et al., 2017).

3.3.3. Suicidal behavior

One study assessing suicidal behavior showed no differences in concentrations of total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides, and total lipids in bipolar depressed patients presenting with suicidal thoughts, suicidal tendencies and making suicidal attempt during the 3 months before admission (Ainiyet and Rybakowski, 2013). Nevertheless, other authors who evaluated a possible relationship between blood lipid levels in patients with BD within 24 hours of their admission and suicide attempts found that average total cholesterol was significantly lower ($p = 0.013$) among suicide attempters than among suicide non-attempters. In addition, suicide attempters had statistically significantly lower triglycerides levels ($p = 0.028$) than non-attempters (Vukusan-Cusa et al., 2009). No statistically significant differences were found between bipolar patients with history of lifetime suicide attempts and bipolar patients without history of suicide attempts in HDL-cholesterol and LDL-cholesterol (Vukusan-Cusa et al., 2009).

Evidence comparing bipolar suicide completers and bipolar controls has shown no significant differences between suicide completers and controls in levels of serum cholesterol on the index hospitalization (Tsai et al., 2002).

3.4. Impaired Glucose Metabolism and Diabetes

3.4.1. Course of episodes

Patients with impaired glucose metabolism (IGM), compared to euglycemic patients, had significant differences in measures of the course of illness in different studies. Specifically, there was a trend to have a longer duration of illness ($p = 0.052$), a higher number of past manic or hypomanic episodes ($p < 0.001$) and a higher number of past mood episodes ($p = 0.03$) (Mansur et al., 2016). A study assessing diabetic inpatients with BD showed that the total number of psychiatric hospitalizations in these subjects was significantly greater than the comparison group ($p < 0.05$) (Cassidy et al., 1999). Another study did not find statistically significant associations between IGM and the number of lifetime episodes, polarity at onset, age at onset of BD, number of lifetime episodes, history of long-term disability, and family or personal history of psychosis during mood episodes (Calkin et al., 2015). However, it reported that bipolar patients with IGM (both insulin resistance and T2DM) more often had a chronic course of the affective illness compared to euglycemic patients ($p = 0.031$) (Calkin et al., 2015), which was supported by a previous study (Ruzickova et al., 2003). IGM was found to be a better predictor of unfavorable course of illness than BMI ($p < 0.001$) (Calkin et al., 2015). However, in another study T2DM was not linked to higher rates of outpatient service use in patients with BD over time (Jerrell et al., 2010).

Further research focused on the correlations between insulin sensitivity and depression severity using the HDRS to assess male inpatients found a significant negative correlation between insulin sensitivity and severity of depressive symptoms ($r = -0.57$, $p = 0.04$) (Hung et al., 2007).

Similarly, other authors assessed the role of IGM as a moderator on the course and severity of BD, showing significant interactions between lifetime mood episodes and IGM on age at onset ($p = 0.037$), illness duration ($p = 0.030$) and episode frequency ($p = 0.026$). However, the association between BD illness duration and lifetime mood episodes was stronger in euglycemic participants. Conversely, the correlation between episode frequency and number of previous mood episodes was significantly stronger in individuals with IGM ($p = 0.029$), relative to euglycemic subjects. There was also a negative correlation between lifetime mood episodes and persistence of depressive symptoms in the euglycemic groups, but a positive correlation in the IGM participants (Mansur et al., 2016).

3.4.2. Rapid cycling

Patients with IGM were reported to have significantly higher rates of rapid cycling than euglycemic patients ($p = 0.012$), which was controlled for present and lifetime use of antipsychotic medication and BMI, entered as covariates in addition to age and gender ($p = 0.039$) (Calkin et al., 2015). This was also supported by previous evidence (Hajek et al., 2008; Ruzickova et al., 2003).

3.4.3. Suicidal behavior

A history of suicide attempts was correlated with a greater number of lifetime mood episodes in euglycemic patients, whereas such difference in the IGM subgroup has not been found (Mansur et al., 2016).

Other research did not find statistically significant differences in blood glucose levels between patients with and without a history of lifetime suicide attempts (Vukusan-Cusa et al., 2009). Lack of association between IGM and suicidal behavior was also found in more recent studies (Calkin et al., 2015). A study assessing risk factors for suicide through a comparison between bipolar suicide completers and controls with BD showed no significant differences between suicide completers and controls in levels of fasting blood sugar on the index hospitalization (Tsai et al., 2002).

3.4.4. Treatment response

Patients with IGM have a poorer response to treatment with lithium (36.8% of T2DM and 36.7% of insulin resistance patients had no

response to lithium vs. 3.2% of healthy patients; $p = 0.035$) (Calkin et al., 2015), and also to other mood stabilizers, such as valproate, lamotrigine and carbamazepine ($p < 0.002$) (Steardo et al., 2019). A study demonstrated that a greater proportion of euglycemic patients achieved remission when treated with lithium (54.8%) compared with those with insulin resistance (23.3%) or T2DM (21.1%), which remained significant ($p < 0.0001$) after controlling for other variables, such as the use of antipsychotic medication or BMI. Response to lithium was negatively associated with a continuous measure of insulin resistance, as estimated by the Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) ($p = 0.013$) (Calkin et al., 2015).

3.4.5. Global functioning

Three independent studies reported significant lower GAF scores in patients with diabetes mellitus or pre-diabetic abnormalities compared to the group of patients without metabolic disturbances (Ruzickova et al., 2003; Leopold et al., 2016).

One study pointed out that quality of life measured with the WHO-5 was significant lower in the group with pre-diabetes/T2DM; there was a trend for lower quality of life in the mental component summary scale and physical component summary scale of the SF-12 (SF-12 mental health: $p = 0.095$; physical health $p = 0.052$) (Leopold et al., 2016). Other authors found a higher percentage of individuals with long-term disability in patients with comorbid T2DM (81%) compared with subjects without T2DM (30%; $p < 0.001$) (Ruzickova et al., 2003).

3.5. Hypertension

3.5.1. Course of episodes

A cohort study found that hypertension was associated with higher rates of outpatient service use in patients with BD ($p < 0.05$). However, service use over time or time to recovery for BD were not increased (Jerrell et al., 2010).

3.5.2. Rapid cycling

In one study, hypertension was not shown to be related to higher rates of rapid cycling (Hajek et al., 2008), but evidence is limited.

3.5.3. Suicidal behavior

Blood pressure parameters have not shown statistically significant differences between bipolar patients with a history of lifetime suicide attempts compared to bipolar patients without a history of suicide attempts (Vukusan-Cusa et al., 2009).

3.5.4. Cognitive functioning

In a study assessing cognitive functioning, hypertension was not related to poorer functioning compared to patients without hypertension (Hajek et al., 2005).

4. DISCUSSION

Patients with BD are more likely to have comorbid metabolic risk factors than the general population, which is directly associated with mortality, quality of life and health care spending. However, the nature of the relationship between BD and metabolic disturbances is complex and so far still not well understood (Sprah et al., 2017).

The current systematic review examined and compared the evidence for different components of metabolic risk as course modifiers of BD. We found 36 observational studies to be included in our review. We rated it according to the AMSTAR system and we found it to be of moderate quality (Shea et al., 2017). No clinical trials were found for inclusion during the systematic literature search.

The scarcity of eligible prospective studies investigating metabolic abnormalities and the course of BD became apparent during the performance of this systematic review. Some excluded studies assessed unipolar and bipolar depressive patients in the same group or

pharmacological response was the main outcome and was different between groups. Additionally, the study designs were heterogeneous, entailing difficulties to compare the outcomes explored between them (Fagioli et al., 2005). Moreover, studies assessed many different outcome measures, which also added a complication to finding evidence within some of them.

Several studies of the relationship between metabolic impairments and the course of illness in BD focused on obesity as the main risk factor for a chronic course of illness, rapid cycling, suicidal behaviors, poorer treatment response to lithium, and global functioning. Obesity showed mixed evidence regarding risk of recurrence (Fagioli et al., 2003; De Almeida et al., 2009; Hu et al., 2017; Goldstein et al., 2013; Bond et al., 2010; Reininghaus et al., 2014) and time until recovery of mood episodes (Bond et al., 2010; Goldstein et al., 2011; McElroy et al., 2016; Post et al., 2014; Calkin et al., 2015; Peters et al., 2016). Disparity of results was also found with respect to risk of rapid cycling in obese patients (Calkin et al., 2015; Buoli et al., 2017; Calkin et al., 2009). In one of the studies (Buoli et al., 2017), a logistic regression showed that obesity before the onset of rapid cycling was a possible predictor of rapid cycling, which supports the hypothesis defending that obesity could be a risk factor for rapid cycling. The last pharmacological treatment was assessed and compared between groups (rapid cycling vs non-rapid cycling), not differing significantly, excepting with asenapine, which was more frequently prescribed in rapid cycling patients ($p < 0.05$). Nevertheless, doses used were not specified and wider information regarding pharmacological treatment among groups was not provided. Body mass index also significantly predicted rapid cycling ($p = 0.013$) in another study (Calkin et al., 2015), but when metabolic factors were entered into a logistic regression, insulin resistance or type 2 diabetes significantly predicted rapid cycling ($p = 0.022$), whereas the effect of BMI was no longer significant ($p = 0.271$).

Statistically significant higher rates of suicide attempts were reported in some studies (Fagioli et al., 2005; Goldstein et al., 2013; Goldstein et al., 2016; Shapiro et al., 2017), whereas another study did not show significant differences (De Almeida et al., 2009) and another assessing weight cycling did not find them either (Reininghaus et al., 2014). A negative correlation between BMI and lithium response was found in one paper (Calkin et al., 2009). These patients therefore required other medications, with the potential side effects of metabolic conditions (weight gain, insulin resistance, DM II and dyslipidemia), which suggests a bidirectionality between the use of drugs and weight gain. Patients with complete remission with lithium showed lower BMI compared to those with no therapeutic effects, which might mean that wellness entails the ability to exercise and follow a healthy diet, with less depressed states which could also alter appetite and lifestyle, and probably also less requirements of antipsychotics, used in acute phases (Calkin et al., 2009). This might explain a worse response to treatment in patients with higher BMI, and not only the BMI by itself. Further studies are needed controlling for different doses, duration of treatment with different medications and other confounding factors, such as adherence to treatment.

Cognitive impairments in obese patients have been reported (Mora et al., 2017; Silveira et al., 2014), but other authors did not find statistically significant differences (Hajek et al., 2005; Bond et al., 2017). Compared to non-obese individuals, obese subjects demonstrated significantly worse global functioning (Goldstein et al., 2013; Goldstein et al., 2011; Calkin et al., 2009), whereas another study found an association between CSWG and impaired 12-month global functioning in females but not in males (Bond et al., 2010).

Studies are also mixed regarding the poorer outcomes for patients with MetS. The presence of MetS was significantly associated with duration of depression and length of time receiving antidepressant medications (Li et al., 2019) and with total number of psychiatric hospitalizations (McIntyre et al., 2010). History of suicide attempts showed inconclusive results (De Almeida et al., 2009; McIntyre et al., 2010; Fagioli et al., 2005). One study showed poorer global functioning in

patients with MetS compared to patients without MetS (Bai et al., 2016), whereas other studies did not find statistically significant differences (Li et al., 2019; De Almeida et al., 2009; Fagioli et al., 2005).

Most studies investigating blood lipid levels focused on suicidal behavior, with one study suggesting that lower total cholesterol and triglycerides levels could predict suicide attempts (Vuksan-Cusa et al., 2009), which could not be confirmed in other studies (Ainiyet and Rybakowski, 2013; Tsai et al., 2002). A statistically significant relationship between hypercholesterolemia and rapid cycling was demonstrated in one study (Buoli et al., 2017). A prospective analysis showed absence of a linear correlation between total cholesterol levels at intake and depressive or manic symptom burden at the follow-up, but it also found a statistically significant, inverse linear effect of cholesterol on manic symptom burden (Fiedorowicz et al., 2010). The symptomatic severity of mania did not show a significant correlation with serum cholesterol or triglycerides levels, whereas the symptomatic severity of depression had a non-significant positive correlation with serum cholesterol levels. Serum triglyceride levels had a significantly negative correlation with BPRS scores (Chung et al., 2007), but this was not assessed in further studies.

Studies investigating IGM were more concordant than studies assessing other metabolic factors. IGM has been found to be a predictor of an unfavorable course of illness in some studies (Calkin et al., 2015; Calkin et al., 2009; Mansur et al., 2016; Cassidy et al., 1999; Hung et al., 2007), including higher rates of rapid cycling (Hajek et al., 2008; Ruzickova et al., 2003; Calkin et al., 2015). This might be a relevant focus in future studies on metabolic conditions and bipolar disorder, given the association found in this article. No significant associations were found between suicidal behavior and IGM (Calkin et al., 2015; Vuksan-Cusa et al., 2009; Tsai et al., 2002). There is a poorer response to mood stabilizers in patients with insulin resistance or T2DM (Calkin et al., 2015; Steardo et al., 2019) and also lower global functioning (Ruzickova et al., 2003; Leopold et al., 2016; Hajek et al., 2005), quality of life (Leopold et al., 2016) and long-term disability (Ruzickova et al., 2003).

Finally, limited evidence assessing the relationship between hypertension and the course of BD suggested that hypertension was not significantly associated with higher rates of outpatient service use (Jerrell et al., 2010), rapid cycling (Hajek et al., 2008), suicidal behavior (Vuksan-Cusa et al., 2009) or lower cognitive functioning (Hajek et al., 2005). However, the paucity of studies suggested that further evidence is required to confirm these findings.

The limitations of this review include small sample sizes, lack of randomized clinical trials and predominance of cross-sectional studies, lack of controlling of confounding factors such as metabolic profile and doses used of pharmacological treatments, lack of comparison of outcomes between different metabolic risk factors, lack of studies assessing the same outcome, not including relevant variables, heterogeneous study designs and very few studies focused on blood pressure as the main factor. Overall, this provided an overall moderate level of evidence.

5. CONCLUSIONS

Although a number of studies regarding the relationship between each metabolic component and outcomes in BD suggest an association between metabolic risk factors and worse course of illness, the evidence assessing each particular outcome is mixed. In addition, the variables assessed by the different authors and the study designs are heterogeneous, and there are possible confounding variables that could not be considered in some papers, which complicates conclusions.

Despite obesity being the most studied risk factor regarding metabolic disturbances, it showed the greatest controversy among the included studies. However, current evidence suggests that metabolic syndrome, obesity and impaired glucose metabolism could be considered risk factors for worse outcomes of BD, such as a chronic course of illness, worse global functioning and rapid cycling. Particularly, this

study suggests that screening the presence of IGM in patients with BD and implementing strategies to prevent and treat this condition might be relevant in order to improve the prognosis of the mental illness.

Future studies with larger sample sizes are required to address these topics with greater depth. New insights in this field could lead to better prevention strategies and thus the improvement of both medical and psychiatric prognoses. In this regard, future research will have to clarify whether there is a predisposition to more severe outcomes of BD consequent on these factors. Trials of weight loss interventions and interventions to manage other metabolic abnormalities could be useful to confirm the causal direction of these factors towards a worse prognosis of BD, and to determine whether an improvement in metabolic measures could act as a disease-modifying treatment. From a clinical perspective, efforts to develop psychosocial interventions and to detect metabolic disturbances during follow-up visits could limit the associated elevated morbidity and mortality in this population and ensure better monitoring and a multidisciplinary treatment, which could secondarily improve the quality of life and psychiatric outcomes of patients with BD.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of Competing Interest

AGP has received CME-related honoraria, or consulting fees from Janssen-Cilag, Angelini and Lundbeck and reports no financial or other relationship relevant to the subject of this article. SGC has received CME-related honoraria, or consulting fees from Janssen-Cilag, Italfarmaco, Angelini and Lundbeck and reports no financial or other relationship relevant to the subject of the present work. SD has received grant support from Stanley Medical Research Institute, NHMRC, Beyond Blue, ARHRF, Simons Foundation, Geelong Medical Research Foundation, Fondation FondaMental, Eli Lilly, Glaxo SmithKline, Organon, Mayne Pharma and Servier. He has received speaker's fees from Eli Lilly, advisory board fees from Eli Lilly and Novartis and conference travel support from Servier. IP has received CME-related honoraria, or consulting fees from ADAMED, Janssen-Cilag and Lundbeck (unrelated to the present work). EV has received grants and served as consultant, advisor or CME speaker for the following entities (unrelated to the present work): AB-Biotics, Abbvie, Angelini, Celon, Dainippon Sumitomo Pharma, Ferrer, Gedeon Richter, GH Research, Janssen, Lundbeck, Otsuka, Sage, Sanofi-Aventis, and Takeda. MB has received Grant/Research Support from the NIH, Cooperative Research Centre, Simons Autism Foundation, Cancer Council of Victoria, Stanley Medical Research Foundation, Medical Benefits Fund, National Health and Medical Research Council, Medical Research Futures Fund, Beyond Blue, Rotary Health, A2 milk company, Meat and Livestock Board, Woolworths, Avant and the Harry Windsor Foundation, has been a speaker for Abbot, Astra Zeneca, Janssen and Janssen, Lundbeck and Merck and served as a consultant to Allergan, Astra Zeneca, Bio-advantex, Bionomics, Collaborative Medicinal Development, Janssen and Janssen, Lundbeck Merck, Pfizer and Servier – all unrelated to this work. The other authors declare no conflicts of interest.

ACKNOWLEDGMENTS

Dr. Vieta thanks the support of the Spanish Ministry of Science and Innovation (PI15/00283, PI18/00805) integrated into the Plan Nacional de I+D+I and co-financed by the ISCIII-Subdirección General de Evaluación and the Fondo Europeo de Desarrollo Regional (FEDER); the Instituto de Salud Carlos III; the CIBER of Mental Health (CIBERSAM); the Secretaria d'Universitats i Recerca del Departament d'Economia i Coneixement (2017 SGR 1365), the CERCA Programme, and the Departament de Salut de la Generalitat de Catalunya for the PERIS grant

SLT006/17/00357. Dr. Pacchiarotti thanks the support of the Spanish Ministry of Science and Innovation (PI18/01001). Dr. Verdolini research is supported by a BITRECS Project, which has received funding from the European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie grant agreement N°754550 and from "La Caixa" Foundation (ID 100010434), under the agreement LCF/PR/GN18/50310006. Dr. Berk is supported by a NHMRC Senior Principal Research Fellowship (1156072).

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.neubiorev.2021.11.026>.

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2. Hipótesis

Hipótesis primarias

1. En el TB, un estilo de vida de mayor calidad en términos de más ejercicio y una dieta más saludable, se asociará con una menor severidad clínica (menos episodios, menor duración de la enfermedad, menos síntomas depresivos, mejor funcionalidad y mayor calidad de vida percibida) y un mejor perfil metabólico **(Estudio I)**.
2. En pacientes con TB, el tratamiento con litio puede contribuir a un aumento de peso moderado, aunque en menor grado que otras alternativas terapéuticas **(Estudio II)**.

Hipótesis secundarias

1. Anticipamos que ciertos tratamientos farmacológicos mostrarán diferentes asociaciones con parámetros metabólicos **(Estudio I)**.

3. Objetivos

Objetivos primarios

1. Caracterizar una muestra representativa de nuestra población de pacientes con TB, en fase de eutimia o con sintomatología depresiva leve, centrándose en hábitos de vida (dieta y ejercicio) y parámetros metabólicos, evaluando la relación de estos factores entre sí y con el curso de la enfermedad **(Estudio I)**.
2. Establecer la evidencia existente de asociación entre los cambios de peso corporal y la monoterapia con litio **(Estudio II)**.

Objetivos secundarios

1. Evaluar los patrones dietéticos de nuestra muestra, con análisis factorial, para caracterizar mejor los hábitos dietéticos de la población a estudio, y examinar sus implicaciones clínicas y metabólicas **(Estudio I)**.
2. Investigar la relación de tratamientos farmacológicos con parámetros metabólicos en nuestra muestra **(Estudio I)**.
3. Comparar el efecto sobre el cambio de peso corporal entre litio, placebo o comparadores activos en pacientes con TB **(Estudio II)**.

4. Material, métodos y resultados

Artículo I

Antecedentes: Los factores de estilo de vida son un área de estudio emergente en el trastorno bipolar (TB) debido a sus posibles efectos tanto en el curso de la enfermedad como en la salud física. El objetivo de este estudio fue describir y explorar conjuntamente las interrelaciones entre los patrones de dieta, el ejercicio, el tratamiento farmacológico con el curso de la enfermedad y el perfil metabólico en pacientes con TB.

Métodos: La muestra consistió en 66 individuos con TB, eutímicos o con síntomas depresivos leves. Se evaluaron de forma transversal parámetros clínicos y metabólicos, así como el tratamiento farmacológico o los hábitos de estilo de vida (dieta y ejercicio). Se exploraron las correlaciones para diferentes interrelaciones y se realizó un análisis factorial de los patrones dietéticos.

Resultados: La adherencia a la dieta mediterránea fue baja, observada en el 37,9% de los pacientes y se asoció positivamente con la calidad de vida percibida. La cantidad de ejercicio se asoció inversamente con los niveles de colesterol, con un 32,8% de los participantes calificados como poco activos según el Cuestionario Internacional de Actividad Física. Se observó una alta prevalencia de obesidad (40,6%) y síndrome metabólico (29,7%). Los usuarios de litio mostraron el mejor perfil metabólico. Curiosamente, se identificaron tres patrones dietéticos: “vegetariano”, “omnívoro” y “Western”. El hallazgo clave fue el impacto positivo general del patrón “vegetariano” en el TB, que se asoció con puntuaciones de depresión reducidas, mejor funcionamiento psicosocial y calidad de vida percibida, disminución del índice de masa corporal, colesterol, LDL y presión arterial diastólica. El consumo de frutos secos se asoció con un mejor perfil metabólico.

Conclusiones: Un patrón de dieta vegetariana se asoció con mejores parámetros clínicos y metabólicos en pacientes con TB. Los estudios futuros deberían priorizar los diseños prospectivos y aleatorizados para determinar relaciones causales y potencialmente informar recomendaciones clínicas.

Is a vegetarian diet beneficial for bipolar disorder? Relationship between dietary patterns, exercise and pharmacological treatments with metabolic syndrome and course of disease in bipolar disorder

Susana Gomes-da-Costa^{1,2,3} | Isabel Fernández-Pérez⁴ | Roger Borrás¹ |
Noelia Lopez² | Yudith Rivas² | Victoria Ruiz² |
Maria Teresa Pons-Cabrera^{2,5} | Anna Giménez-Palomo^{1,2} | Gerard Anmella^{1,2} |
Marc Valenti^{1,2} | Michael Berk⁶ | Eduard Vieta^{1,2} | Isabella Pacchiarotti^{1,2}

¹Bipolar and Depressive Disorders Unit, Institute of Neuroscience, Hospital Clinic, University of Barcelona, IDIBAPS, CIBERSAM, Barcelona, Spain

²Department of Psychiatry and Psychology, Institute of Neurosciences, Hospital Clinic, Barcelona, Spain

³Sant Andreu Mental Health Care Centre, Vidal i Barraquer Foundation, Barcelona, Spain

⁴Neuroscience Research Group, Hospital del Mar Research Institute, Barcelona, Spain

⁵Health and Addictions Research Group, Institute of Neuroscience, Hospital Clinic, University of Barcelona, IDIBAPS, Barcelona, Spain

⁶IMPACT—The Institute for Mental and Physical Health and Clinical, Translation, School of Medicine, Food and Mood Centre, Barwon Health, Deakin University, Geelong, Victoria, Australia

Correspondence

Isabella Pacchiarotti, Bipolar and
Depressive Disorders Unit, Hospital
Clinic, University of Barcelona, Institute
of Neuroscience, IDIBAPS, CIBERSAM,
170 Villarroel st, 12-0, 08036, Barcelona,
Catalonia, Spain.
Email: pacchiar@clinic.cat

Abstract

Background: Lifestyle factors are being increasingly studied in bipolar disorder (BD) due to their possible effects on both course of disease and physical health. The aim of this study was to jointly describe and explore the interrelations between diet patterns, exercise, pharmacological treatment with course of disease and metabolic profile in BD.

Methods: The sample consisted of 66 euthymic or mild depressive individuals with BD. Clinical and metabolic outcomes were assessed, as well as pharmacological treatment or lifestyle habits (diet and exercise). Correlations were explored for different interrelations and a factor analysis of dietary patterns was performed.

Results: Adherence to the Mediterranean diet was low, seen in 37.9% of the patients and was positively associated with perceived quality of life. The amount of exercise was negatively associated with cholesterol levels, with 32.8% of participants rated as low active by International Physical Activity Questionnaire. There was a high prevalence of obesity (40.6%) and metabolic syndrome (29.7%). Users of lithium showed the best metabolic profile. Interestingly, three dietary patterns were identified: “vegetarian,” “omnivore” and “Western.” The key finding was the overall positive impact of the “vegetarian” pattern in BD, which was associated with reduced depression scores, better psychosocial functioning, and perceived quality of life, decreased body mass

index, cholesterol, LDL and diastolic blood pressure. Nuts consumption was associated with a better metabolic profile.

Conclusions: A vegetarian diet pattern was associated with both, better clinical and metabolic parameters, in patients with BD. Future studies should prioritize prospective and randomized designs to determine causal relationships, and potentially inform clinical recommendations.

KEYWORDS

bipolar disorder, diet, exercise, mental health, metabolic syndrome, nutrition

1 | INTRODUCTION

Bipolar disorder (BD) is a chronic mood disorder characterized by mood fluctuations, affecting a wide range of population. It usually begins at a young age and can lead to functional impairment, disability, and socio-economic burden.^{1,2} Long term treatment is needed, yet many patients remain resistant to current treatments, presenting residual symptoms that contribute to an important functional impairment.³

Some of the most widely used pharmacological treatments especially antipsychotics can contribute to metabolic disturbances, increased food intake, weight change or sedentary behavior.^{4,5} These factors contribute for a high prevalence of physical health issues in patients with BD. The prevalence of metabolic syndrome and other cardiovascular problems is therefore higher in this group than in the general population.^{6–8} Finally, these patients have shown an increased risk of premature mortality.⁹ Furthermore, these medical conditions may have a negative impact on the course of the illness.¹⁰

Patients with BD show lower levels of physical exercise compared to the general population, with a trend towards sedentarism.^{11,12} This trend may be attributed to factors including the nature of the disease itself, pharmacological treatments, or depressive episodes, among others. Additionally patients tend to have poorer dietary habits,¹³ and functional impairment might complicate the preparation of foods, while other barriers such as limited access to healthy foods or socioeconomic problems may contribute.^{14,15} Sedentary habits as well as poor diet may be associated with depressive symptoms and a worse outcome of BD.¹⁶

Recently, the field of lifestyle and nutritional psychiatry has attracted much evidence and scientific interest,^{17–19} evaluating associations between lifestyle and course of disease¹³ as potentially modifiable risk factors. Mediterranean diet pattern is one of the most studied patterns in relation with mental disorders, is characterized by a high consumption of fruits, vegetables, unrefined cereals, olive oil, nuts,

Significant outcomes

- Metabolic syndrome was described on 29.7% and obesity in 40.6% of our sample with BD.
- Mediterranean diet was positively associated with perceived quality of life and physical activity was negatively associated with cholesterol levels.
- Positive impact on mental and metabolic health, was found with a “vegetarian diet” pattern, derived by factorial analysis.

Limitations

- The cross-sectional design of this study cannot reveal causal dynamics between variables.
- The moderate sample size limited the statistical power.
- There is a lack of previous evidence about vegetarian diet impact on BD.

and sea food; moderate consumption of chicken, dairy products, and red wine; and low consumption of red meat, and have shown beneficial effects, especially on depression and anxiety and cardiovascular health.²⁰ Nuts consumption, has shown also potential beneficial effects in depressive symptoms and cardiovascular health.^{21–23} Lifestyle factors, especially dietary patterns, appear associated with an increased severity of BD symptoms.²⁴ In patients with BD, greater consumption of plant-based foods and fish products was inversely related to physical and psychiatric symptoms.²⁵ Less frequent weekly exercise in BD patients was associated with worse metabolic and clinical outcomes.²⁶ Nutritional or lifestyle interventions may have utility,^{16,27} together with usual therapies as pharmacological treatment or psychotherapy, in reduction of mental symptoms, especially depression and improvement of metabolic variables.^{17,18,28}

Nevertheless, there remains a significant gap in understanding which dietary patterns, correlate with impacts on course of disease or metabolic profiles in BD. Only a few studies have concurrently assessed both lifestyle factors and the prevalence of metabolic syndrome, along with their correlation with the course of the disease and pharmacological treatment.²⁴ Furthermore, limited research has examined the impact of dietary patterns on BD patients, utilizing factor analysis—a statistical technique increasingly utilized in the field of nutritional epidemiology.^{25,29,30}

The goal of this observational study was to characterize euthymic or mild depressive BD patients, focusing on lifestyle habits (diet and exercise) and metabolic parameters, evaluating the relationship of these factors with the course of disease and the pharmacologic interactions. Additionally, we aimed to evaluate dietary patterns of our sample, with factor analysis, to better characterize dietary habits and its clinical and metabolic implications. We hypothesized that a higher quality lifestyle in terms of more exercise and a healthier diet, would be associated with a decreased clinical severity and a better metabolic profile. Furthermore, we anticipated that certain treatments might exhibit associations with metabolic parameters.

2 | MATERIALS AND METHODS

2.1 | Study design

This was an observational, cross-sectional study, examining the relationship between dietary patterns with the level of physical activity, metabolic variables, pharmacological treatment, and the course of the disease in a given population, with BD.

Approval to conduct the study was received from the local Ethics Review Board (CEIM-Comité de Ética de Investigación del Hospital Clínic de Barcelona, approval number HCB/2019/0524), and all protocols related to human experiments were conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants after they had received a complete description of the study. Data was anonymous and each patient was assigned an identification code.

2.2 | Patient population

Participants were recruited from the Hospital Clinic of Barcelona outpatient clinic, between July 2019 and October 2023. Subjects in this analysis met the following

inclusion criteria: (1) patients diagnosed with bipolar disorder type I and II (DSM5); (2) adults (> 18 years old); and (3) euthymia or mild depression, according depression rating scales (Hamilton <16 or Montgomery <18).^{31,32} Subjects were excluded if they met any of the following criteria: (1) current active psychotic symptoms; (2) active substance use disorder (except tobacco); or (3) organic mental illness or major medical comorbidity that might interfere with physical activity.

2.3 | Data collection and study measures

Personal and family medical history on medical-surgical, psychiatric (DSM5 diagnosis), substance use, cardiovascular and metabolic problems; course of the disease, age of diagnosis, duration, number and type of episodes, number of hospitalizations, suicide attempts and a history of psychotic symptoms; socio-demographic data on age, gender, educational level, occupation and marital status, were collected to all study subjects, after obtaining informed consent.

Subjects underwent baseline measurements of blood pressure, anthropometrics, and body fat distribution. Waist circumference was measured from patients at minimal respiration at the smallest circumference of the waist. Height and body weight were measured in light clothing, without jackets or shoes. Blood tests performed in the last 6 months as routine evaluation were used to assess metabolic parameters as glycemia, cholesterol and triglycerides.

Body mass index (BMI) was calculated as weight (kg) divided by height (m²). Individuals were considered underweight if their BMI was <18.5, of normal weight if their BMI was 18.5–24.9, overweight if their body mass index was 25–29.9 and obese if their BMI was ≥30.

Metabolic syndrome was defined as presenting three or more of the following criteria³³:

1. Elevated waist circumference: >102 cm in men and >88 cm in women;
2. Elevated triglycerides (drug treatment for elevated triglycerides is an alternate indicator): ≥150 mg/dL (1.7 mmol/L);
3. Reduced HDL-C (drug treatment for reduced HDL-C is an alternate indicator): <40 mg/dL (1.04 mmol/L) in men and < 50 mg/dL (1.29 mmol/L) in women;
4. Elevated blood pressure (antihypertensive drug treatment in a patient with a history of hypertension is an alternate indicator): systolic ≥130 and /or diastolic ≥85 mmHg;
5. Elevated fasting glucose (drug treatment of elevated glucose is an alternate indicator): ≥100 mg/dL.

To evaluate neuropsychiatric variables, clinician-administered evaluation scales for depression, the Montgomery-Asberg Depression Rating Scale (MADRS),³⁴ and the Hamilton Rating Scale for Depression-17 (HAM-D-17)³⁴ were used to assess the severity of depressive symptoms; the clinician-administered evaluation scale for mania, Young Mania Rating Scale (YMRS)³⁵ was used to evaluate manic symptoms; the clinician-administered evaluation scale for psychosocial functioning, the Functioning Assessment Short Test (FAST)³⁶ was used to assess psychosocial functioning. The FAST scale comprises 24 items, each item rated from 0 (no difficulty) to 3 (severe difficulty). Higher scores indicate worse functioning, and according to total score patients can be categorized.³⁷

Lifestyle factors were evaluated by different scales: dietary intake information was collected using a 45-item food-frequency questionnaire (FFQ) validated for the Spanish population (CFCA),³⁸ participants indicated their average frequency of consumption of food items for during the previous 12 months using specified categories, for number of times/week and times/month, also a self-administered scale of adherence to the Mediterranean diet PREDIMED (MEDAS 14)³⁹ was used. Well-being was assessed with the well-being short self-reported index (WHO-5, Spanish version available at "<http://www.who-5.org>"). Finally a self-administered physical activity questionnaire was used to assess physical activity levels in patients—the International Physical Activity Questionnaire (IPAQ),⁴⁰ consisting of seven questions, that categorizes individuals into three activity levels: low, moderate and high.

2.4 | Statistical analysis

All the data were analyzed using R. Continuous variables were presented as the means $\pm$ SD. Categorical variables were presented as frequencies and percentages.

To determine the relationship between clinical variables and lifestyle factors in patients with BD, Spearman correlation test, Fisher's exact test or Wilcoxon rank sum test were used, according to the type and distribution of the data. A multivariate logistic regression model was used to evaluate the association between different psychopharmacological treatments and metabolic variables. For all analyses, the significance level was set as $p < 0.05$.

For dietary patterns elucidation, the 45-item FFQ³⁸ was segmented into 17 food groups based on nutrient similarity (Appendix Table A1). Subsequently, an exploratory factor analysis was conducted to identify dietary patterns from the food consumption data.^{29,41} This statistical technique aggregates specific food groups based on

their correlations within the dataset, aiming to uncover common underlying patterns (factors). Factors were determined using the minimum sum of squared residuals, with oblimin rotation applied for interpretation. Factor loadings, indicating the strength of association between food groups and dietary patterns, were calculated. Loadings exceeding 0.3 were considered meaningful and used to describe and label the dietary patterns.

Three patterns were identified based on the variance explained by successive components of the food score matrix. Three scores were then assigned to each patient, representing the correlation of their food habits with each dietary pattern. Finally, the association between metabolic and clinical variables and dietary patterns in each patient was assessed using Spearman correlation, Wilcoxon rank sum, or Kruskal-Wallis tests, as appropriate.

3 | RESULTS

3.1 | Patient characteristics

We included 66 euthymic or mild depressive patients with BD. Sociodemographic and clinical variables are presented in Table 1. BD patients had a mean age of 49.6 ± 14.0 ; and 65.2% (43/66) were female. The mean FAST scale score was 28.1 corresponding to mild impairment, these results were also analyzed for subcategories, 16.9% (11/65) patients showed no impairment, 13.8% (9/65) minimal impairment, 36.9% (24/65) mild impairment, 16.9% (11/65) moderate impairment and 15.4% (10/65) presented severe functional impairment.

In relation with metabolic variables, waist circumference mean was above the recommended reference values. Mean BMI was 28.4, also over the recommended range values. Analysis by subgroups revealed 37.5% (24/64) patients in the "normal weight" group (BMI 18.5–24.99), 21.9% (14/64) of the patients were "overweight" (BMI 25–29.9) and 40.6% (26/64) patients were in the "obese" range (BMI ≥ 30). Finally metabolic syndrome was detected in 29.7% (19/64) of the sample.

Psychopharmacological treatments are listed in Table 1. Most patients, 95.4% (62/65), received at least one mood stabilizer and 66.2% (43/65) were treated with at least one antipsychotic.

The lifestyle characteristics of the patients are noted in Table 2. According to the MEDAS scale only 37.9% (25/66) of the patients showed a Mediterranean pattern diet, scoring ≥ 9 points. In relation to physical activity, almost one third of the sample, 32.8% (21/64) scored on the low activity level range.

TABLE 1 Sociodemographic and clinical variables.

		N
Demographic		
Age, mean (SD)	49.6 (14.0)	66
Female gender, <i>n</i> (%)	43 (65.2)	66
Post-secondary education, <i>n</i> (%)	58 (83.2)	65
Clinical characteristics		
BD I, <i>n</i> (%)	39 (60.9)	64
BD II, <i>n</i> (%)	25 (39.1)	64
Age of onset, mean (SD)	32.7 (13.2)	63
Duration of illness, mean (SD)	16.9 (10.9)	63
Lifetime number of depressive episodes, mean (SD)	7.60 (6.42)	62
Lifetime number of manic episodes, mean (SD)	2.39 (4.05)	62
Lifetime number of hypomanic episodes, mean (SD)	3.69 (6.30)	62
Hospitalizations, mean (SD)	2.13 (2.11)	62
Clinical measures		
HAMD-17, mean (SD)	5.36 (4.48)	64
MADRS, mean (SD)	6.75 (5.86)	64
YMRS, mean (SD)	0.81 (1.77)	64
WHO, mean (SD)	12.4 (4.84)	65
FAST, mean (SD)	28.1 (15.4)	65
Anthropometric/metabolic measures		
BMI, mean (SD)	28.4 (6.10)	64
Waist circumference female, mean (SD) cm	95 (17.45)	43
Waist circumference male, mean (SD) cm	106.53 (13.38)	23
Triglycerides, mean (SD) mg/dL	151 (95.8)	60
Cholesterol, mean (SD) mg/dL	188 (37.5)	57
Glucose, mean (SD) mg/dL	99.3 (26.0)	59
Diastolic pressure, mean (SD) mmHg	78.2 (11.8)	65
Systolic pressure, mean (SD) mmHg	121 (15.2)	65
Metabolic syndrome, ³³ <i>n</i> (%)	19 (29.7)	64
Psychotropic treatments		
Mood stabilizers, <i>n</i> (%)	62 (95.4)	65
Valproico, <i>n</i> (%)	19 (29.2)	65
Litio, <i>n</i> (%)	37 (56.9)	65
Carbamacepine, <i>n</i> (%)	3 (4.62)	65
Gabapentine, <i>n</i> (%)	2 (3.08)	65
Lamotrigine, <i>n</i> (%)	16 (24.6)	65
Oxcarbacepine, <i>n</i> (%)	2 (3.12)	64
Antipsychotics, <i>n</i> (%)	43 (66.2)	65
Quetiapine, <i>n</i> (%)	27 (42)	65
Olanzapine, <i>n</i> (%)	4 (6.2)	65
Aripiprazol, <i>n</i> (%)	15 (23)	65
Others, <i>n</i> (%)	3 (4.6)	65
Antidepressants, <i>n</i> (%)	22 (34)	65
Anxiolytics, <i>n</i> (%)	16 (24.6)	65

Abbreviations: BD, Bipolar disorder; BMI, Body mass index; FAST, Functioning Assessment Short Test; HAMD-17, Hamilton Rating Scale for Depression-17; MADRS, Montgomery-Asberg Depression Rating Scale; YMRS, Young Mania Rating Scale; WHO, Well-being short self-reported index.

3.2 | Clinical characteristics and lifestyle

The relationship between diet, exercise and pharmacological treatments with metabolic syndrome and course of disease is summarized in Tables 3 and 4.

A simple correlation analysis indicated a significant association between some lifestyle, clinical and metabolic parameters in BD patients, in Table 3. The WHO score was positively associated with MEDAS scores, that indicate a relation between greater adherence to a Mediterranean diet and better perceived quality of life.

TABLE 2 Lifestyle variables.

Diet and exercise		N
BEDS, mean (SD)	12.1 (7.19)	66
MEDAS <9, n (%) (low adherence to Mediterranean diet)	41 (62.1%)	66
MEDAS ≥9, n (%) (high adherence to Mediterranean diet)	25 (37.9%)	66
IPAQ		
Low activity category, n (%)	21 (32.8%)	64
Moderate activity category, n (%)	33 (51.6%)	64
High activity category, n (%)	10 (15.6%)	64
METS, mean (SD)	1623 (1671)	65

Abbreviations: BEDS, Barcelona Bipolar Eating Disorder Scale; IPAQ, International Physical Activity Questionnaire; MEDAS, self-administered scale of adherence to the Mediterranean diet PREDIMED; METS, metabolic equivalents.

The total amount of exercise, measured by total METS was negatively associated with cholesterol levels. Correlations were found between higher nuts consumption, measured by the FFQ, with reduced BMI, cholesterol and waist circumference. Correlations were not found between adherence to Mediterranean diet according to the MEDAS score nor amount of exercise measured by METS, with other clinical variables as total number of episodes, hospitalizations, MADRS, HAMD-17 or YMRS scores.

Considering the effects of pharmacological treatment, some differences were found in relation with different metabolic variables, represented in Table 4. Treatment with lithium was negatively associated to triglycerides (TG) levels. Antipsychotics were positively associated with an increased waist circumference, BMI, and TG levels. Finally, valproate was positively associated with greater BMI, metabolic syndrome, and TG levels. Due to a small sample size the comparisons were established between patients with or without a specific treatment (lithium, valproate, and antipsychotics), however caution is required in the interpretation since some patients were on multiple treatments at any time (Appendix Table A2). After performing a multivariate analysis, the association between antipsychotics with increased BMI (estimate 4.075, Std. Error 1.535, $p = 0.010$) and increased waist circumference (estimate 11.458, Std. Error 4.276, $p = 0.009$), remained statistically significant, independently from other treatments.

TABLE 3 Correlation coefficients between lifestyle and diet characteristics with clinical and metabolic parameters.

Variables	Lifestyle		
	MEDAS	METS	Nuts week consumption by FFQ
Metabolic			
Cholesterol	−0.0259	0.0184*	0.0396*
Triglycerides	−0.0945	−0.1677	−0.2293
BMI	−0.0352	−0.1501	0.0257*
Waist circumference	−0.1534	−0.0022	0.0193*
Clinical			
WHO	0.0192*	0.2022	0.0723
Number of episodes	−0.0341	−0.0707	0.0925
Number of Hospitalizations	0.0822	0.2048	−0.1761
MADRS	−0.1922	−0.1412	0.0647
HAMD-17	−0.1867	−0.2213	−0.0165
YMRS	−0.0059	−0.0733	−0.1220

Abbreviations: BMI, body mass index; FFQ, Food frequency questionnaire; HAMD-17, Hamilton Rating Scale for Depression-17; MADRS, Montgomery-Asberg Depression Rating Scale; MEDAS, self-administered scale of adherence to the Mediterranean diet PREDIMED; METS, metabolic equivalents; WHO, Well-being short self-reported index; YMRS, Young Mania Rating Scale.

* p -value ≤ 0.05.

TABLE 4 Metabolic differences among psychopharmacological treatments.

Variables	Cholesterol mean (SD)	Triglycerides mean (SD)	BMI mean (SD)	Waist circumference mean (SD)	Systolic blood pressure mean (SD)	MetS %
Treatment						
Lithium wo/w	190.2 (37.8)/186.9 (37.8)	182.8 (125.1)/129.3 (0.031)*	29.6 (7.6)/27.4 (4.7)	100.3 (19.7)/101.3 (14.0)	124.2 (15.7)/118.8 (14.7)	37%/24%
Valproate wo/w	187.6 (40.8)/189.9 (29.3)	127.8 (63.2)/204.1 (0.006)*	27.3 (5.4)/31.1 (7.0)*	98.3 (16.0)/107.2 (16.8)	117.7 (13.8)/129.5 (0.004)**	22%/50%*
Antipsychotics wo/w	174.7 (39.2)/195.6 (35.0)	105.3 (58.0)/173.4 (0.001)***	25.3 (4.6)/30.0 (0.004)**	92.5 (16.0)/105.5 (0.007)*	116.5 (14.7)/123.5 (15.1)	18%/36%

Abbreviations: MetS, metabolic syndrome; w, with; wo, without.
p*-value ≤0.05; *p*-value ≤0.005; ****p*-value ≤0.001.

3.3 | Dietary patterns

An exploratory factor analysis was performed considering the information collected through FFQ, identifying three major dietary patterns. Loading factors of food groups across these major patterns are presented in Figure 1 and explained 33.2% of variation (Appendix Table A3). The “Western diet” pattern was loaded by intake of refined grains, sweets, dairy desserts, potatoes, and alcohol; the “omnivore diet” pattern in which red meat, poultry, fish, dairy and grains predominated; finally, the “vegetarian diet” pattern was rich in fruit, vegetables, eggs, nuts, and pulses. The labels given to the dietary patterns do not entirely describe each underlying pattern, but they are helpful when analyzing and discussing the results.

According to the different dietary patterns significant associations were found with different clinical and metabolic variables, in Table 5. The “vegetarian diet” pattern was associated with reduced depression scores on the HAMD-17, increased WHO scores, reduced FAST scores, reduced weight, reduced BMI, reduced cholesterol, LDL and diastolic blood pressure.

On the other hand, the “omnivore diet” pattern was associated with higher WHO scores and diastolic blood pressure. Correlations with other clinical parameters as total number of episodes or hospitalizations were not found, nor any association with the “Western diet” pattern.

4 | DISCUSSION

Our study aimed firstly at characterizing our BD population, specifically euthymic and mild depressive patients, in terms of different lifestyle, clinical and metabolic factors. We found the average BMI was higher than recommended, with 40.6% of the patients falling in the “obesity” range (BMI ≥30), even higher rates than in previous studies, that described obesity in 29%–35% of the patients.^{42,43} This is especially relevant because overweight and obesity adversely impacts metabolic health but also clinical outcomes,^{44,45} as well as cognitive function compared to normal weight individuals with BD, especially regarding executive functions.⁴⁶

Furthermore, metabolic syndrome was present in 29.7% of our sample, in line with previous studies as Vancampfort's systematic review and meta-analysis, that showed a pooled metabolic syndrome prevalence of 31.0% (95% CI: 24.5%–37.9%).⁷ This is especially relevant, given the potential implications of metabolic syndrome, obesity, and impaired glucose metabolism as risk factors for adverse outcomes in BD. These may include, a chronic course of illness, worse global functioning,

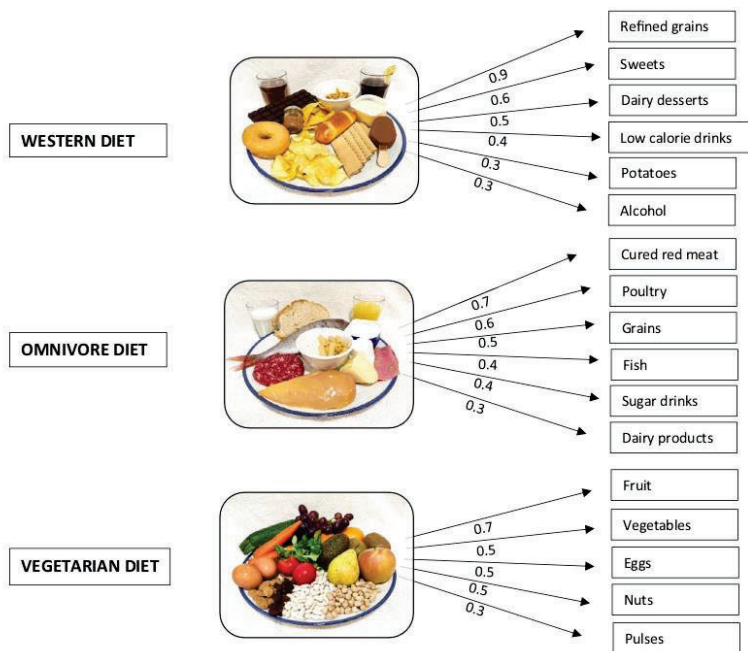


FIGURE 1 Factor analysis of dietary patterns according food frequency questionnaire. Three major dietary patterns identified among our sample: (1) “Western diet” pattern characterized by intake of refined grains, sweets, dairy desserts, potatoes, and alcohol; (2) “omnivore diet” pattern containing red meat, poultry, fish, dairy and grains and 3) “vegetarian diet” pattern rich in fruit, vegetables, eggs, nuts, and pulses.

Variables	Western diet	Omnivore diet	Vegetarian diet
HAMD-17	0.0152	0.0020	0.0168*
MADRS	0.0082	−0.1206	−0.2110
YMRS	0.1261	−0.0089	−0.1999
WHO	0.0391	0.0134*	0.0274*
FAST	0.0594	0.0784	0.0183*
BMI	0.0676	0.1454	0.0351*
Waist circumference	0.1314	0.1535	−0.2263
Cholesterol	0.1996	−0.0079	0.0470*
LDL	0.1377	0.0113	0.0312*
HDL	0.1191	0.0955	0.2373
Triglycerides	0.0588	−0.1399	−0.1777
Glycemia	0.1017	−0.0086	−0.0947
Systolic blood pressure	0.1069	0.1794	−0.1359
Diastolic blood pressure	0.2159	0.0039*	0.0022**

Abbreviations: BMI, body mass index; FAST, Functioning Assessment Short Test; HAMD-17, Hamilton Rating Scale for Depression-17; MADRS, Montgomery-Asberg Depression Rating Scale; WHO, Well-being short self-reported index; YMRS, Young Mania Rating Scale.

p*-value ≤0.05; *p*-value ≤0.005.

TABLE 5 Correlation coefficients between diet patterns with clinical and metabolic parameters.

reduced quality of life and rapid cycling,^{6,47,48} as well as poorer cardiovascular and physical health, with increased premature mortality rates.¹⁰

According to the FAST scale, 32.3% of patients presented moderate to severe impairment, and the mean WHO-5 scores were 12.4, with poor wellbeing defined as

below 13. Together these factors could contribute to difficulties in following a healthy diet or adhering to a regular exercise routine.¹⁴ It is important to consider that our sample scored predominantly euthymic or mild depressive, reason why the potential impact of functioning and perceived quality of life could be independent of the depressive symptomatology, and possibly present on an inter-episodic way, potentially explaining some of the difficulties experienced by these patients, even in absence of active episodes.

Regarding to the Mediterranean diet, there was a low adherence rate, aligning with previous studies that have described a tendency towards poor dietary patterns among this group of patients.^{13,30} Concerning physical activity, nearly one third of the sample were rated as low active by IPAQ, reflecting the prevalence of sedentarism on BD.¹² Moreover, associations were found between adherence to the Mediterranean diet and a higher perceived quality of life, while the amount of physical activity was linked to lower cholesterol levels.

Nut consumption, in accordance with previous literature, was found to be related with better metabolic parameters.²¹ Nonetheless, there was no evident correlation between nut consumption and depressive symptoms, as described previously.²³

Patients receiving valproate showed a positive association with BMI, metabolic syndrome proportion, and TG levels.⁴ Also, patients on antipsychotics had increased waist circumference, BMI, TG levels, and FAST scores concordant with the literature.⁵ Finally, patients treated with lithium had a negative association with TG levels, consistently with prior research. Additionally, even though not statistically significant, a negative association trend was observed with other metabolic parameters such as BMI, weight, or waist circumference, in patients receiving lithium.^{49–52}

After conducting a multivariate analysis, only the association between antipsychotics and increased BMI, as well as increased waist circumference, remained statistically significant, independent of other treatments. The trend of positive metabolic outcomes associated with lithium use was not statistically significant, which could be due to the small sample size.⁵³

The evaluation of diet and its impact in patients with BD has received limited attention, with the most of studies focusing on the relationship between diet and other mental disorders such as anxiety and depression.⁵⁴ Most of studies were initially centered on individual nutrients or well-defined dietary patterns as Mediterranean diet impact. In this study, dietary patterns were evaluated by an exploratory factor analysis, identifying three different dietary patterns in patients with BD, based on the dietary data collected: “vegetarian” pattern, “omnivore” pattern

and “Western” pattern. Most correlations were found within the “vegetarian” pattern, showing both better clinical and metabolic outcomes.

Most prior studies focused on fish, omega 3 consumption or Mediterranean diet adherence,¹³ showed an inverse association between healthy eating habits and symptoms of depression,⁵⁵ consistent across countries and cultures. According previous literature, food patterns potentially associated with reduced risk of depression are those highlighting seafood, vegetables, fruits and nuts, meanwhile a high consumption of refined foods and sugars were significantly associated with depression.⁵⁶

Regarding the vegetarian diet impact on depression, there are contradictory information,⁵⁷ and to our knowledge there are no evidence about vegetarian diet impact on BD. Nonetheless the finding that our “vegetarian” pattern had a positive impact on metabolic status is consistent with epidemiologic studies, reporting that plant-based diets are associated with better cardiovascular outcomes with lower blood pressure, lower blood lipids, reduced platelet aggregation, and a beneficial effect in weight management, reducing the risk of developing metabolic syndrome, type 2 diabetes, cerebrovascular disease, ischemic heart disease or even reducing cancer risk.⁵⁸

Our study supports the emergent field of diet and lifestyle intervention in patients with BD, stressing the importance of explore dietary habits and physical activity level of our patients in clinical practice, allowing to detect subgroups of patients whose could benefit from individual or group lifestyle intervention.¹⁶

Regarding the limitations of this study, it should be noted that is a cross sectional study without longitudinal follow-up nor control group, the scales used to evaluate diet and exercise habits were self-reported, without objective measures of exercise or diet. In addition to the stated limitations, the moderate sample size limited the statistical power.⁵³ Multiple comparisons mean that findings should be regarded as exploratory. Also, as discussed above, dietary patterns differ across populations and cultural contexts, making it difficult to draw comparisons. Moreover, medication could be a confounding factor.⁵⁹ The study aimed to describe dietary patterns in patients with BD and to elucidate the relationship between dietary patterns and course of disease and metabolic variables but did not attempt to show an effect of dietary patterns on patients with BD, considering that an association obtained from a cross sectional study does not necessarily indicate causality. It is also important to note that we are assessing dietary patterns obtained through factor analysis and their relationships with other variables. There's a distinction between assessing the clinical and metabolic implications of our “vegetarian diet” pattern

and examining those same implications in patients who are following a vegetarian diet.

However, the present study had several strengths. Our observational cross-sectional study jointly evaluates both lifestyle factors, prevalence of metabolic syndrome and its correlation with the course of the disease and pharmacological treatment. Also, to our knowledge, is the first in the Spanish population to analyze the association of dietary patterns with BD, which is important as there are marked differences in the dietary profiles of different countries in Eastern and Western Europe. There are advantages in using dietary patterns in nutritional epidemiology instead of analyzing individual foods and nutrients. Dietary patterns analysis takes account of interactions between nutrients, thus allowing consideration of the effect of the whole diet.²⁹ Finally, in contrast to previous studies our research aims to jointly describe and explore the interrelations between diet, exercise, pharmacological treatment with the course of disease and metabolic health. This approach is crucial considering that all these factors operate together and interact.

To Conclude, our study revealed a high prevalence of metabolic syndrome and obesity in BD. Adherence to the Mediterranean diet was low, yet positively correlated with perceived quality of life. Conversely, level of physical activity was negatively associated with cholesterol levels, with nearly one-third of our sample classified as low active. Finally considering the specific analysis of dietary patterns the main finding was the global positive impact of our “vegetarian diet” pattern in both clinical and metabolic outcomes, as well as the positive impact of nuts consumption on metabolic profile.

These data could potentially pave the way for new research hypotheses. Large-scale randomized clinical trials should be conducted, to confirm the association between high-quality vegetarian or plant-based diet patterns, lower risk of depression and better metabolic health in patients with BD. Moreover, the finding of a high prevalence of obesity and metabolic syndrome, and a low adherence to healthy lifestyle habits, underscores the importance of developing and implementing, tailored interventions addressing modifiable lifestyle factors, such as exercise and diet, aimed at enhancing both mental and physical health.

ACKNOWLEDGEMENTS

We are extremely grateful to all the participants. We thank the Vidal i Barraquer Foundation for the time and support. Also, we thank Joan Jiménez Balado for statistical support. The authors thank the support of the Instituto de Salud Carlos III (PI21/00787) the Secretaria d'Universitats i Recerca del Departament d'Economia i Coneixement (2021-SGR-01358), CERCA Programme, Generalitat de Catalunya; La Marató-TV3 Foundation

grants 202234-30; the European Union Horizon 2020 research and innovation program (H2020-EU.3.1.1.—Grant No 754907, H2020-EU.3.1.3.—Grant 945151, HORIZON.2.1.1.—Grant 101057454) and EIT Health (EDIT-B project). GA is supported by a Juan Rodés 2023 grant (JR23/00050), a Rio Hortega 2021 grant (CM21/00017) and Acción Estratégica en Salud-Mobility (M-AES) fellowship (MV22/00058), from the Spanish Ministry of Health financed by the Instituto de Salud Carlos III (ISCIII) and co-financed by the Fondo Social Europeo Plus (FSE+). GA thanks the support of the Spanish Ministry of Health financed by the Instituto de Salud Carlos III (ISCIII) and co-financed by the European Social Fund+ (ESF+) (JR23/00050, MV22/00058, CM21/00017); the ISCIII (PI21/00340, PI21/00169); the Milken Family Foundation (PI046998); the Fundació Clínic per a la Recerca Biomèdica (FCRB)—Pons Bartan 2020 grant (PI04/6549), the Sociedad Española de Psiquiatría y Salud Mental (SEPSM); the Fundació Vila Saborit; and the Societat Catalana de Psiquiatria i Salut Mental (SCPISM). MB is supported by a NHMRC Leadership 3 Investigator grant (GNT2017131). The authors received no financial support for the research, authorship, or publication of this article.

CONFLICT OF INTEREST STATEMENT

SGC has received CME-related honoraria, or consulting fees from Janssen-Cilag, Italfarmaco, Angelini, Rovi, Takeda and Lundbeck and reports no financial or other relationship relevant to the subject of this article. MTP has received financial support for CME activities and travel funds from Lundbeck, Pfizer, and Esteve, with no financial or other relationship relevant to this work. AGP has received CME-related honoraria or consulting fees from Angelini, Janssen-Cilag, Casen Recordati, Rovi, LCN and Lundbeck, and reports no financial or other relationship relevant to the subject of this article. GA has received CME-related honoraria, or consulting fees from ADAMED, Angelini, Casen Recordati, Janssen-Cilag, Lundbeck, Lundbeck/Otsuka, Rovi, and Viatrix, with no financial or other relationship relevant to the subject of this article. MV has received research grants from Eli Lilly & Company and has served as a speaker for Abbott, Bristol-Myers Squibb, GlaxoSmithKline, Janssen-Cilag, and Lundbeck. MB has received Grant/Research Support from the NIH, Cooperative Research Centre, Simons Autism Foundation, Cancer Council of Victoria, Stanley Medical Research Foundation, Medical Benefits Fund, National Health and Medical Research Council, Medical Research Futures Fund, Beyond Blue, Rotary Health, A2 milk company, Meat and Livestock Board, Woolworths, Avant and the Harry Windsor Foundation, has been a speaker for Abbot, Astra Zeneca, Janssen and Janssen, Lundbeck and Merck and served as a consultant to

Allergan, Astra Zeneca, Biadvantex, Bionomics, Collaborative Medicinal Development, Janssen and Janssen, Lundbeck Merck, Pfizer and Servier – all unrelated to this work. EV has received grants and served as consultant, advisor or CME speaker for the following entities (unrelated to the present work): AB-Biotics, Abbott, Abbvie, Adamed, Angelini, Beckley Psychtech, Biogen, Biohaven, Boehringer Ingelheim, Intracellular, Casen-Recordati, Celon, Compass, Dainippon Sumitomo Pharma, Ethypharm, Ferrer, Gedeon Richter, GH Research, Glaxo Smith-Kline, Idorsia, Janssen, Johnson & Johnson, Lundbeck, Luye, Newron, Novartis, Organon, Otsuka, Rovi, Sage, Sanofi-Aventis, Sunovion, Takeda, Teva, and Viatrix. IP has received CME-related honoraria, or consulting fees from Janssen-Cilag, Lundbeck, Lundbeck/Otsuka, CASEN Recordati and Angelini, with no financial or other relationship relevant to the subject of this article. The rest of the authors report no biomedical financial interests or potential conflicts of interest related to the present article.

PEER REVIEW

The peer review history for this article is available at <https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/acps.13733>.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Susana Gomes-da-Costa  <https://orcid.org/0000-0003-0383-0555>

Gerard Anmella  <https://orcid.org/0000-0002-6798-4054>

Michael Berk  <https://orcid.org/0000-0002-5554-6946>

Eduard Vieta  <https://orcid.org/0000-0002-0548-0053>

Isabella Pacchiarotti  <https://orcid.org/0000-0002-7822-0367>

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How to cite this article: Gomes-da-Costa S, Fernández-Pérez I, Borrás R, et al. Is a vegetarian diet beneficial for bipolar disorder? Relationship between dietary patterns, exercise and pharmacological treatments with metabolic syndrome and course of disease in bipolar disorder. *Acta Psychiatr Scand.* 2024;1-14. doi:10.1111/acps.13733

APPENDIX A

TABLE A1 Categorization of the 45-item FFQ into food groups.

Food groups	Food items
Cured and red meats	Red meat (beef, pork, and lamb) and minced meat
Poultry	Chicken and turkey
Fish	White fish, blue fish, and seafood
Eggs	Eggs
Dairy products	Milk, yogurt, cheese
Dairy desserts	Custard, flan, ice cream
Fruit	Citrus fruits, fruit, and fresh fruit juice
Nuts and dried fruit	Almonds, hazelnuts, walnuts, peanuts
Vegetables	Salad: lettuce, tomato, endive, carrots Green beans, chard, spinach, garlic, Garnish vegetables: eggplant, mushrooms
Pulses	Beans, peas, lentils, soy
Potatoes	Potatoes, chips
Grains	White breads, pasta, rice, pies, pizza
Refined grains	Breakfast cereals, cookies, muffins
Sweets and desserts	Chocolates, cakes, cream cakes, donuts, jams, candies, jelly beans
Sugary drinks	Soft drinks, commercial fruit juice
Low calorie drinks	Low-calorie soft drinks, beer without alcohol
Alcohol	Wine, sangria, beer, Whisky, gin, cognac

TABLE A2 Treatment subgroups.

Treatment	N (%)
AP	7 (10.8%)
LT	14 (21.5%)
VP	3 (4.6%)
LT + AP	20 (30.8%)
VP + AP	13 (20%)
LT + VP	0 (0%)
AP + LT + VP	3 (4.6%)
None	5 (7.7%)

Abbreviations: AP, antipsychotics; LT, lithium; VP, valproate.

	Western diet	Omnivore diet	Vegetarian diet
Dairy products	0.218	0.307	0.205
Sweets	0.611	−0.125	0.356
Grains	0.125	0.513	
Refined grains	0.880		
Pulses		0.317	0.323
Eggs	−0.212	0.398	0.481
Vegetables	−0.114		0.513
Poultry	−0.128	0.578	0.167
Cured red meat	0.141	0.687	−0.205
Fish		0.397	0.286
Fruit		−0.121	0.664
Dairy desserts	0.464	0.133	−0.212
Potatoes	0.340	0.200	
Sugar drinks		0.371	−0.257
Low drinks	0.439	0.162	
Alcohol	0.313		0.108
Nuts			0.457
Variance explained (%)	11.5	10.8	10

TABLE A3 Factor loadings for the different food groups for each dietary pattern (N = 66).

Artículo II

Antecedentes: El litio sigue siendo el tratamiento de mantenimiento de referencia para el trastorno bipolar (TB). Sin embargo, el aumento de peso es un efecto secundario de creciente relevancia debido a sus implicaciones metabólicas.

Métodos: Realizamos una revisión sistemática y un metaanálisis destinado a resumir la evidencia sobre el uso de litio y el cambio de peso en el TB. Seguimos la metodología PRISMA, buscando en Pubmed, Scopus y Web of Science.

Resultados: De 1003 referencias examinadas, 20 estudios se incluyeron en la revisión sistemática y 9 en el metaanálisis. En línea con los estudios incluidos en la revisión sistemática, el metaanálisis reveló que el aumento de peso con litio no fue significativo, notando un aumento de peso de 0,462 kg ($p = 0,158$). Una duración más corta del tratamiento se asoció significativamente con un mayor aumento de peso. En comparación con placebo, no hubo diferencias significativas en el aumento de peso. El aumento de peso fue significativamente menor con litio, que con comparadores activos.

Conclusiones: Este trabajo revela un bajo impacto del litio en el cambio de peso, especialmente en comparación con algunos de los comparadores activos más utilizados. Estos resultados podrían influir en las decisiones clínicas, aportando información importante tanto para terapeutas como pacientes.



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Neuroscience and Biobehavioral Reviews

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Lithium therapy and weight change in people with bipolar disorder: A systematic review and meta-analysis

Susana Gomes-da-Costa^a, Wolfgang Marx^b, Filippo Corponi^c, Gerard Anmella^a,
 Andrea Murru^a, Maria Teresa Pons-Cabrera^a, Anna Giménez-Palomo^a,
 Felipe Gutiérrez-Arango^a, Cristian Daniel Llach^a, Giovanna Fico^a, Georgios D. Kotzalidis^d,
 Norma Verdolini^a, Marc Valenti^a, Michael Berk^b, Eduard Vieta^{a,*}, Isabella Pacchiarotti^a

^a Bipolar and Depressive Disorders Unit, Institute of Neuroscience, Hospital Clinic, University of Barcelona, IDIBAPS, CIBERSAM, 170 Villarroel St, 12-0, 08036, Barcelona, Spain

^b Deakin University, IMPACT – the Institute for Mental and Physical Health and Clinical Translation, School of Medicine, Barwon Health, Geelong, Australia

^c School of Informatics, University of Edinburgh, Edinburgh, United Kingdom

^d Department of Neurosciences, Mental Health and Sensory Organs (NESMOS), Sapienza University of Rome, School of Medicine and Psychology, Sant'Andrea University Hospital, Via di Grottarossa 1035-1039, 00189, Rome, Italy

ARTICLE INFO

Keywords:

Lithium
 Bipolar disorder
 Weight gain
 Mood stabilizers
 Depression
 Mania
 Mood disorders
 Psychiatry
 Neurosciences

ABSTRACT

Lithium remains the gold standard maintenance treatment for Bipolar Disorder (BD). However, weight gain is a side effect of increasing relevance due to its metabolic implications. We conducted a systematic review and meta-analysis aimed at summarizing evidence on the use of lithium and weight change in BD. We followed the PRISMA methodology, searching PubMed, Scopus and Web of Science. From 1003 screened references, 20 studies were included in the systematic review and 9 included in the meta-analysis. In line with the studies included in the systematic review, the meta-analysis revealed that weight gain with lithium was not significant, noting a weight increase of 0.462 Kg ($p = 0.158$). A shorter duration of treatment was significantly associated with more weight gain. Compared to placebo, there were no significant differences in weight gain. Weight gain was significantly lower with lithium than with active comparators. This work reveals a low impact of lithium on weight change, especially compared to some of the most widely used active comparators. Our results could impact clinical decisions.

1. Introduction

Bipolar Disorder (BD) is a chronic disorder characterized by recurrent mood fluctuations. It is associated with both high morbidity and mortality (Carvalho et al., 2020), hence long-term prophylactic maintenance treatment is recommended (Vieta et al., 2011). Lithium, introduced in 1949 (Cade, 1949), remains probably the most effective drug for long-term therapy in BD, preventing both depressive and manic recurrences and reducing the risk of suicide, dementia and all-cause mortality (Geddes et al., 2004; Del Matto et al., 2020; Severus et al., 2014; Miura et al., 2014). It is consequently recommended as first line treatment in most guidelines (Yatham et al., 2018; Malhi et al., 2015; Grunze et al., 2013; Verdolini et al., 2020), either as monotherapy or combination (Wingård et al., 2019).

Despite the long-term effectiveness of lithium, there are concerns regarding its safety profile. Aside from the narrow therapeutic index, the need for monitoring, and some frequent side effects such as diarrhea, polydipsia and tremor, lithium's toxicity profile includes an increased risk of renal failure and reduced urine-concentrating ability, hypothyroidism, hyperparathyroidism, and weight gain (McKnight et al., 2012; Tondo et al., 2017).

Weight gain is among the most distressing lithium-associated side effects for patients (Gitlin, 2016). In one study, despite ranking third in frequency, it ranked first among patients' rating of bothersome side effects of lithium use and second amongst bothersome side effects leading to lithium discontinuation (Gitlin et al., 1989). Nevertheless, weight gain remains as one of the less studied complications related with lithium treatment. Besides this, there is a high prevalence of weight gain

* Corresponding author at: Bipolar and Depressive Disorders Unit, Hospital Clinic, University of Barcelona, Institute of Neuroscience, IDIBAPS, CIBERSAM, 170 Villarroel st, 12-0, 08036, Barcelona, Catalonia, Spain.

E-mail address: EVITA@clinic.cat (E. Vieta).

<https://doi.org/10.1016/j.neubiorev.2021.07.011>

Received 3 May 2021; Received in revised form 9 July 2021; Accepted 10 July 2021

Available online 13 July 2021

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and weight-related conditions due to other medications used to treat BD. Among these, metabolic syndrome (around 37 %) (Vancampfort et al., 2013), obesity (around 21 %) (Krishnan, 2005), type 2 diabetes mellitus (around 14 %) and non-alcoholic fatty liver disease (22–42 %) are prominent (Soto-Angona et al., 2020; Vancampfort et al., 2016). These associated comorbidities lead to cardiovascular disease and higher premature mortality in BD patients (Correll et al., 2017; Staudt Hansen et al., 2019; Kessing et al., 2015; Hayes et al., 2015). People with BD who suffer weight-gain and related comorbidities also have a worse clinical course, more depression, associated physical comorbidities, and higher suicide rates (Hayes et al., 2015; Fagioli et al., 2003; Torrent et al., 2008).

To date, findings about lithium-induced weight gain are controversial and inconsistent (Gitlin, 2016; McKnight et al., 2012). In fact, definitions of weight change and duration of observation differ across studies, precluding any simple averaging of lithium-induced weight gain. From the available studies, it is also unclear whether weight gain correlates with lithium dose or levels (Gitlin, 2016). Furthermore, the majority of studies include BD patients concurrently treated with psychotropic medications other than lithium, such as antipsychotics, valproate, and some antidepressants, which might contribute to weight gain (Torrent et al., 2008). Finally, genetic factors may be much more relevant than lithium itself (Bopp et al., 2019).

In this context, lithium-induced weight change is of increasing scientific and clinical interest for both patients and practitioners, considering that weight gain is usually one of the most dreaded side effects for patients and that in many occasions, it is the main reason for treatment discontinuation (Gitlin et al., 1989).

To provide evidence-based information for decision-making and accurate information to patients and professionals, the primary aim of this study is to systematically investigate whether lithium induces weight change and, if so, to quantify the magnitude of this association, compared to active comparators or placebo. The secondary aim of this study is to examine whether lithium-induced weight change is moderated by duration of lithium therapy.

2. Methods

This review was conducted according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement (Moher et al., 2009) followed by the Meta-analyses of Observational Studies in Epidemiology (MOOSE) (Stroup et al., 2000); the review protocol was registered on PROSPERO database (Registration number: CRD42020144702).

2.1. Search strategy

A search strategy was developed based on the research question, according to the PICO format (Table 1) (Miller, 2001).

Studies were identified using the following databases: MEDLINE/PubMed, Scopus, and Web of Science from any time to August 1st 2019. The systematic search was performed by four independent researchers blinded to each other's results (SGC, AGP, MPC, and FGA).

The following search strategy was used in PubMed and then adapted for Scopus and Web of Science: (bipolar disorder[Mesh] OR bipolar disorder*[TI] OR bipolar I disorder[TI] OR bipolar II disorder[TI] OR bipolar-I[ti] OR bipolar-II[ti] OR mania[TI] OR manic[TI]) AND

(lithium[Mesh] OR lithium[TI]) AND (weight[ALL] OR triglyceride*[ALL] OR cholesterol[ALL] OR HDL[ALL] OR VLDL[ALL] OR LDL[ALL] OR glycated hemoglobin OR glycated haemoglobin* OR BMI OR body mass index OR blood glucose OR plasma glucose OR plasma lipids OR blood lipids OR serum lipids); no restrictions were applied. Finally, the reference lists of relevant identified papers were hand-searched for further relevant studies.

After completing the searches, duplicate studies were removed, four independent investigators (SGC, AGP, MPC and FGA) screened independently the titles and abstracts for eligibility. A list of potentially eligible studies was developed by consensus, and the full texts were assessed by the above two teams. Both teams then applied eligibility criteria and developed a final list of studies to include. A fifth investigator (FC) supervised the process; any divergences were dealt through consensus.

2.2. Study selection

We included longitudinal studies evaluating the effect of lithium on weight change. Randomized controlled trials (RCTs) comparing lithium with placebo, or other active comparators in patients with BD were included. Prospective cohort studies comparing patients with and without lithium treatment and cross-over studies were also considered. No restriction on study time length or language were applied. Studies including parameters related to weight were sought (i.e., BMI, weight in kg or lb; the latter was converted to kg).

We excluded animal, *in vitro*, and cell culture studies, as well as those on the effects of drugs on body weight involving lithium, but not reporting results for each drug separately, absence of a lithium monotherapy arm, or lithium administered only as adjunctive therapy. Other exclusion criteria were reviews, editorials, opinion papers, letters-to-the-editor providing no original data, studies reporting on the same sample as other published studies, selective data reporting, duplicates, congress/conference abstracts, non-peer reviewed journals or papers, studies not reporting effects on body weight and related measures or studies involving other diagnoses than BD. Meta-analyses and reviews were used as evidence to support information that could not be drawn from individual studies.

For each outcome, all studies meeting inclusion criteria were assessed and tabulated for the narrative systematic review, but only the highest available form of evidence as RCTs were included in the formal meta-analysis.

2.3. Outcomes and data extraction

The main outcomes investigated were those related with body weight change: baseline and follow-up weight (kg or lb), baseline and follow-up BMI, weight change from baseline (kg or lb), BMI change from baseline, percentage of weight change (%), and clinically significant change in bodyweight (>7% total weight in kg).

An independent search and extraction of data according to an *a priori* data extraction checklist were performed independently and in duplicate by the aforementioned four investigators. The following information was extracted: first author; year of publication; study design; study duration; country where the study was conducted; bipolar disorder subtype (I or II) if stated; mood status; sample size; weight change in lithium and control groups after treatment (endpoint minus baseline weight); lithium doses and blood levels; duration of treatment; active comparator or placebo, active comparator doses and blood levels when applicable. For all measures, when available, standard deviation (SD) and standard error (SE) were extracted.

2.4. Quality assessment of the included studies

We rated the quality of eligible studies through the assessment of their risk of bias, using the Cochrane Collaboration Risk of Bias tool 2.0

Table 1

Search strategy based on the research question, according to the PICO format.

Parameter	Criteria
Population	Human participants clinically diagnosed with Bipolar Disorder.
Intervention	Lithium monotherapy.
Comparator	Placebo or active comparator.
Outcomes	Weight change and related metabolic measures.

(RoB) (Sterne et al., 2019). We classified each study into a high, low, unclear risk category arising from the randomization, intervention adherence (deviation from intended interventions), missing outcome data, outcome measurement, and selective reporting domains, which in turn affected the overall quality of the study.

2.5. Data synthesis and statistical analysis

The meta-analyses were conducted in Comprehensive Meta-Analysis 3.01 using a random-effects model to account for heterogeneity between studies. Effect sizes were presented as differences in means (Kg) (with 95 % confidence intervals (CI)). The following outcomes were explored in separate analyses: (i) The difference in weight in people with BD receiving lithium at follow up compared to baseline, (ii) The difference in weight change in people receiving lithium compared to placebo or other active treatments (only compared against active treatments that are recommended for maintenance treatment of BD). As an additional analysis, we also performed a subgroup analysis to study if trial duration influenced the treatment effect. Given the paucity of available data, we

were unable to conduct the planned analysis on the effect of lithium treatment on other metabolic parameters as BMI, glucose, triglycerides and cholesterol. Heterogeneity was assessed with I^2 test. Significance was set at $p < 0.05$.

3. Results

3.1. Search strategy

The search flow-diagram and the main results are reported in Fig. 1. MEDLINE/Pubmed search produced 375 records, Scopus yielded 438 and Web of Science 467. Twelve additional records were identified through other sources/reference lists. All eligible studies were incidentally in English. Of 714 unduplicated records, after screening by title or abstract, 63 full-text articles were retrieved and assessed for eligibility. Of these, 43 articles were excluded. Reasons for exclusion are provided in Fig. 1.

The remaining 20 articles (Findling et al., 2019; Gao et al., 2018; Yaramala et al., 2020; Amsterdam et al., 2016; Hayes et al., 2016;

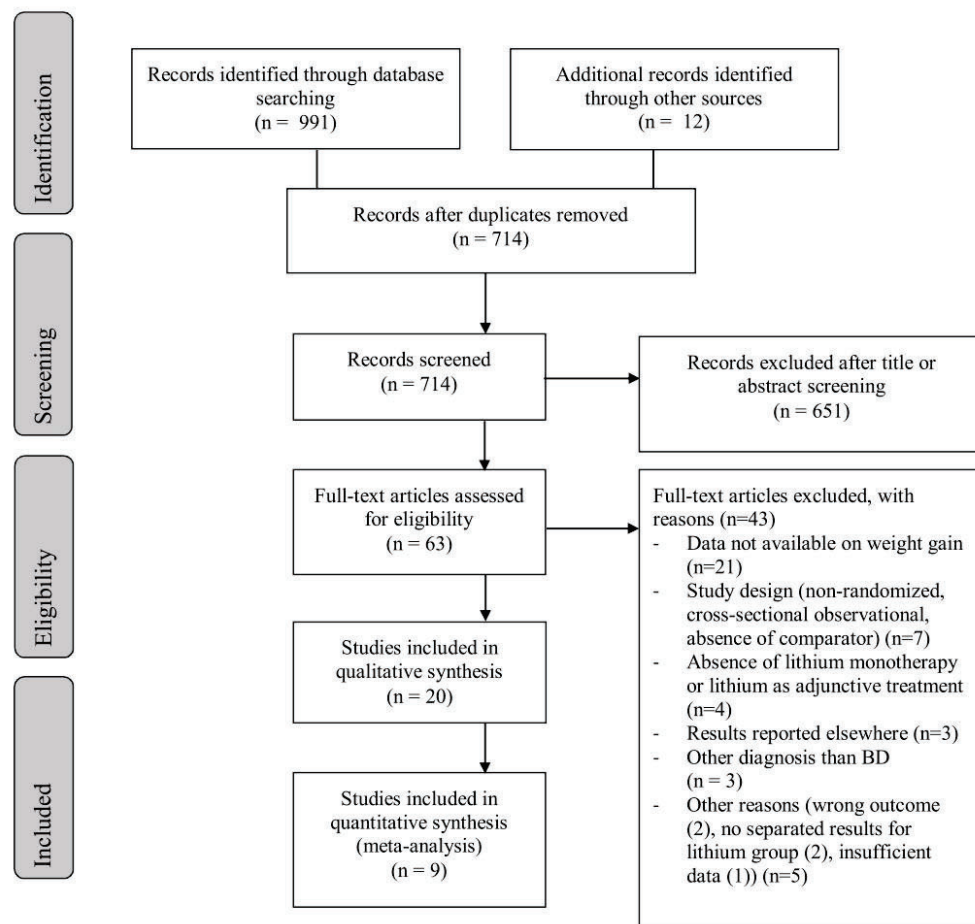


Fig. 1. PRISMA Flow diagram of the included studies.

Findling et al., 2015; Geller, 2012; McIntyre et al., 2011; Bowden et al., 2010; Keck et al., 2009; Amsterdam and Shults, 2008; Niufan et al., 2009; Bowden et al., 2008; Tohen et al., 2005; Bowden et al., 2005; Calabrese et al., 2005, 2003; Bowden et al., 2003, 2000; Peselow et al., 1980) reported qualitative information on weight change with lithium treatment compared to placebo and/or active comparator; these were suitable for the narrative synthesis. Of them, 9 articles (Findling et al., 2019; Gao et al., 2018; Yaramala et al., 2020; Amsterdam et al., 2016; Findling et al., 2015; Geller, 2012; Bowden et al., 2010; Keck et al., 2009; Tohen et al., 2005) were suitable for the meta-analysis and were included.

3.2. Characteristics of studies included in the systematic review

The characteristics of the included studies in the systematic review, together with a narrative synthesis of the study results and the quality assessment with the Cochrane Collaboration Risk of Bias tool 2.0 (RoB), of the appraised evidence are reported in Tables 2 and 3.

The 20 studies included a total of 10,812 participants with BD (3844 following treatment with lithium, 6372 with active comparator and 596 with placebo). Regarding BD subtype, 10 studies were on BD I, 2 studies on BD II and 8 studies on either both or undefined. Mood status was reported as manic or mixed episode in 13 studies, depressive in 3 studies and both or undefined in 4 studies (Table 2). Sample sizes for each study ranged from 31 to 6671 participants. The age of the participants ranged from 10 to 44 years.

Of the included studies, 18 studies were RCTs, some of them with an open label acute treatment phase prior to a double blind maintenance phase and 2 were prospective cohort studies (Hayes et al., 2016; Peselow et al., 1980). All but three studies, which focused on children and adolescents (Findling et al., 2019, 2015; Geller, 2012) were conducted in adult populations with BD. Active comparators included quetiapine (Gao et al., 2018; Yaramala et al., 2020; Hayes et al., 2016; Bowden et al., 2005), venlafaxine (Amsterdam et al., 2016; Amsterdam and Shults, 2008), divalproex or sodium valproate (Hayes et al., 2016; Geller, 2012; Bowden et al., 2010, 2008; Calabrese et al., 2005; Bowden et al., 2000), olanzapine (Hayes et al., 2016; Niufan et al., 2008; Tohen et al., 2005), risperidone (Geller, 2012), aripiprazole (McIntyre et al., 2011; Keck et al., 2009), and lamotrigine (Calabrese et al., 2003; Bowden et al., 2003).

The weight change measures from baseline were very heterogeneous among studies, including: 1) mean weight change from baseline 2) BMI, 3) body weight at different timepoints (baseline, end of the study, different weeks); 4) proportion of patients with clinically relevant (>7% from baseline) weight gain or loss, 5) proportion of patients with >15% weight gain, 6) proportion of patients presenting weight gain or loss as an adverse effect/event, 7) change in weight z score (change score is the week value minus the baseline value; baseline is defined as the first visit of the efficacy phase mean $\pm$ SD), 8) mean weight change by baseline BMI category (<23 kg/m², 23–27 kg/m² or >27 kg/m²).

Most studies reported, to a variable extent, some degree of weight gain with lithium, but few stated the statistical significance of weight change. Eight studies showed a greater weight gain with the active comparator than with lithium therapy (Yaramala et al., 2020; Hayes et al., 2016; Geller, 2012; Bowden et al., 2010; Niufan et al., 2008; Tohen et al., 2005; Bowden et al., 2005, 2000), 4 studies did not show significant differences in weight gain between lithium and active comparators (McIntyre et al., 2011; Keck et al., 2009; Calabrese et al., 2005; Bowden et al., 2003), and 3 studies showed greater weight gain with lithium than active comparators (Amsterdam et al., 2016; Amsterdam and Shults, 2008; Bowden et al., 2003). Six studies found no statistically significant difference in weight gain between lithium and placebo (Findling et al., 2019, 2015; Bowden et al., 2005; Keck et al., 2009; Bowden et al., 2005; Calabrese et al., 2003; Bowden et al., 2000), while only one study found increased weight gain with lithium compared to placebo (Peselow et al., 1980).

3.3. Characteristics of studies included in the meta-analysis

The 9 studies included in the meta-analysis were all RCTs, and had a total of 2212 participants (991 following treatment with lithium, 1014 with active comparator and 207 with placebo). Sample sizes for each study ranged from 31 to 482 participants, and study durations varied from 8 to 52 weeks. The age of participants ranged from 10 to 43 years.

3.4. Results of the meta-analysis

We reported the results according to the different weight change comparisons investigated:

3.4.1. Weight change during lithium treatment

3.4.1.1. Weight change during lithium treatment: difference in means of kg, at follow up compared to baseline. A total of 9 studies, comprising 9 unique comparisons and 991 participants, were included for these meta-analyses, reported in Fig. 2, (Findling et al., 2019; Gao et al., 2018; Yaramala et al., 2020; Amsterdam et al., 2016; Findling et al., 2015; Geller, 2012; Bowden et al., 2010; Keck et al., 2009; Tohen et al., 2005). Details of the studies assessed can be found in Tables 2 and 3.

The difference in weight between lithium treated patients at follow up compared to baseline did not reach statistical significance, reporting weight gain of 0.462 Kg in the lithium group (Difference in means = 0.462, 95 % C.I. = -0.179 to 1.103, $p = 0.158$, $n = 991$). Heterogeneity for this outcome was high ($I^2 = 89\%$).

3.4.1.2. Weight change during lithium treatment according to trial length.

A subgroup analysis was performed to examine whether lithium weight change was moderated by duration of lithium therapy and is reported in Fig. 3. Weight gain was significantly greater in those interventions with 12 weeks or shorter, (Difference in means = 0.552, 95 % C.I. = 0.010–1.095, $p = 0.046$).

3.4.2. Differences in weight change in people receiving lithium compared to active controls or placebo

3.4.2.1. Weight change with lithium compared to placebo. A total of 3 studies, comprising 3 unique comparisons and 437 participants ($n = 230$ lithium, $n = 207$ placebo), were included for these meta-analyses reported in Fig. 4 (Findling et al., 2019, 2015; Keck et al., 2009). Details of the studies assessed can be found in Tables 2 and 3.

The difference in weight between lithium and placebo at follow up from baseline did not reach statistical significance, favoring weight loss in the lithium group (Difference in means = -0.354, 95 % C.I. = -1.011 to 0.303, $p = 0.291$, $n = 437$). Heterogeneity for this outcome was $I^2 = 0.0\%$.

3.4.2.2. Weight change in lithium-treated groups compared with weight change in active comparators. A total of 5 studies, comprising 6 unique comparisons and 1411 participants ($n = 663$ lithium, $n = 748$ active comparators), compared weight change between lithium treatment and active comparators (Amsterdam et al., 2016; Bowden et al., 2010; Geller, 2012; Keck et al., 2009; Tohen et al., 2005). Details of the studies assessed can be found in Tables 2 and 3.

Considering that antidepressants are not considered as maintenance treatment in monotherapy for BD in general, a sensitivity analysis excluding the study with venlafaxine as active comparator (Amsterdam et al., 2016), was performed and reported in Fig. 5, resulting in a significant difference, favoring weight gain in the active comparator group of 1.446 kg, compared to lithium group (Difference in means = -1.446, 95 % C.I. = -2.489 to -0.404, $p = 0.007$, $I^2 = 86.8$, $n = 1282$).

Table 2

Summary of studies included in the systematic review and meta-analysis.

First author and publication year	Duration (weeks)	Treatment groups Drug, n	Mean (SD)/median/[range] dose mg/d	Mean (SD)/median/[range] serum concentration mEq/L	Diagnosis	Mood status	Age: mean (SD)	Gender: % Female
Studies entering the meta-analysis								
Yaramala et al., 2020	24 weeks	(1) LI + APT, n = 240 (2) QTP + APT, n = 242	(1,2) NA (secondary analysis of Bipolar CHOICE study)	(1,2) NA	BD I and BD II	Different mood status considered	38.6 (12.1) LI, 39.1 (12.2) QTP	58.3 LI, 59.1 QTP.
Findling et al., 2019	28 weeks	(1) LI, n = 17 (2) placebo, n = 14	(1) 1412 (428)	(1) 0.8–1.2	BD I	Manic or mixed episode	12 (2.5)	32
Gao et al., 2018	16 weeks	(1) LI, n = 18 (2) QTP, n = 24	(1) 600 (2) 327.78, [100–900]	(1) 0.5 [0.3–1.05] (n = 13), second lithium levels 0.8 [0.4–1] (n = 7) (1) mean max level 0.94 (0.38), [0.30–2.40]	BD I, BD II or subthreshold BD	Different mood status considered	39.48 (14.69)	52.4
Amsterdam et al., 2016	12 weeks	(1) LI, n = 64 (2) VLF, n = 65	(1) mean max dose 1180.85 (399.14), [300–1800] (2) mean max dose 256.55 (101.07), [75–375]	(1) mean max level 0.94 (0.38), [0.30–2.40]	BD II	Depressive episode	42.9 (13.6)	56.6
Findling et al., 2015	8 weeks	(1) LI, n = 53, (2) placebo, n = 28	(1) 1483 (584), median (min-max) 1500 (300–3600)	(1) 0.98 (0.47)	BD I	Manic or mixed episode	11.5 (2.9) LI, 11.2 (3.0) placebo	58.5 LI, 46.4 placebo
Geller, 2012	8 weeks	(1) LI, n = 90 (2) RSP, n = 89 (3) VLP, n = 100	(1) NA (2) 2.57 (1.21) (3) NA	(1) 1.09 (0.34) (2) NA (3) 113.6 (23.0) µg/mL	BD I	Manic or mixed episode	10.1 (2.8)	50.2
Bowden et al., 2010	12 weeks	(1) LI, n = 135 (2) VLP, n = 122	(1) 969 (207) (2) 1394 (394)	(1) 0.8 (0.3) (2) 114 (136) µg/mL	BD I	Manic or mixed episode	38.5 (12.6)	63 LI, 54 VLP
Keck et al., 2009	12 weeks	(1) LI, n = 160, (2) APZ, n = 155 (3) placebo, n = 165.	(1) 1210.6 (2) 23.6	(1) 0.66 (0.27)	BD I	Manic or mixed episode.	39.6 (10.5) LI, 39.6 (10.6) APZ, 39.8 (11.3) placebo	48 LI, 49 APZ, 48 placebo
Tohen et al., 2005	52 weeks	(1) LI, n = 214 (2) OLZ, n = 217	(1) 1102.7 (270.3) (2) 11.9 (4.4)	(1) 0.76 (0.14)	BD	Manic or mixed episode	42.3 (12.3) LI, 42.5 (13.1) OLZ	53.7 LI, 52.1 OLZ.
Studies entering only the systematic review								
Hayes et al., 2016	18 years, Jan. 1995 to Dec. 2013	(1) LI, n = 2148, (2) VLP, n = 1670, (3) OLZ, n = 1477, (4) QTP, n = 1376.	(1,2,3,4) NA	(1,2,3,4) NA	BD	Mood status not defined	46.29 LI, 42.31 VLP, 41.01 OLZ, 38.08 QTP	59.92 LI, 54.55 VLP, 53.55 OLZ, 69.69 QTP
McIntyre et al., 2011	52 weeks (12+40)	(1) LI, n = 38 (2) APZ, n = 25	(1) [1119.5–1211.7] (2) 21.7 [20.8–23.9]	(1,2) NA	BD I	Manic or mixed episode	41.21 (9.84) LI, 37.20 (11.85) APZ	50 LI, 60 APZ
Amsterdam and Shults, 2008	12 weeks	(1) LI, n = 40 (2) VLF, n = 43	(1) 966.24 (410.9), [0–2400] (2) 185.6 (92.04), [0–450]	(1) 0.64 (0.265), [0.29–1.5]	BD II	Depressive episode	37.2 (13.4)	57
Niufan et al., 2008	4 weeks	(1) LI, n = 71 (2) OLZ, n = 69	(1) 1110 (257.4), median (IQR) 1114 (950.0–1296.4) (2) 17.8 (2.56), median (IQR) 18.8 (16.4–19.7)	(1,2) NA	BD	Manic or mixed episode	32.6 (13.21)	52.9
Bowden et al., 2008	12 weeks	(1) LI, n = 149 (2) VLP, n = 149	(1) 1052 (298), median (range) 1000 (400–1600) (2) 1618 (366), median (range) 1500 (750–3000)	(1) median (range) 0.68 (0.0–1.92) (2) median (range) 57.9 µg/mL (2.1–122)	BD I	Manic episode	43.6 (12.4)	54

(continued on next page)

Table 2 (continued)

First author and publication year	Duration (weeks)	Treatment groups Drug, n	Mean (SD)/median/[range] dose mg/d	Mean (SD)/median/[range] serum concentration mEq/L	Diagnosis	Mood status	Age: mean (SD)	Gender: % Female
Bowden et al., 2005	12 weeks	(1) LI, n = 98 (2) QTP, n = 107 (3) placebo, n = 95	(1) [400–800] (2) 586 prior to day 21 and 618 prior to day 84.	(1) mean target (0.6–1.4) Median 0.73 at day 14, 0.80 at day 21, and 0.80 at day 84.	BD I	Manic episode	Age (range): 38.8 (18–73) LI, 38 (18–72) QTP, 41.3 (18–70) placebo	40.8 LI, 43.9 QTP, 42.1 placebo
Calabrese et al., 2005	80 weeks	(1) LI, n = 32 (2) VLP, n = 28	(1) 1359, [900–2100] (2) 1571, [750–2750]	(1) 0.92 (2) 77 µg/ml	BD I or BD II disorder, rapid cycling	Hypomanic, manic, or a mixed episode	37.2 (9) LI, 37 (8.2) VLP	59 LI, 43 VLP
Calabrese et al., 2003	76 weeks	(1) LI, n = 120 (2) LTG, n = 169 (3) placebo, n = 121.	(1) median (range) 900 (450–1800) (2) median (range) 200 (100–285)	(1) 0.8 (0.3)	BD I	Depressive episode.	43.6 (12.3) LI, 44.1 (11.7) LTG, 42.1 (13) placebo	60 LI, 59 LTG, 50 placebo
Bowden et al., 2003	76 weeks	(1) LI, n = 46 (2) LTG, n = 58 (3) placebo, n = 69.	(1) NA (2) [100–400]	(1) [0.8–1.1]	BD I	Hypomanic or manic episode	41.9 (11.3) LI, 40.6 (12.6) LTG, 40.9 (11.0) placebo	52 LI, 55 LTG, 51 placebo
Bowden et al., 2000	52 weeks	(1) LI, n = 90, (2) VLP, n = 187, (3) placebo, n = 92	(1,2,3) NA	(1) 1.0 (0.48), median (min-max) 0.9 (0.1–2.7) (2) 84.8 (29.9), median (min-max) 83.9 (0.6–156) µg/ml	BD I	Manic episode	40.3 ± 9.8 LI, 38.9 ± 12.7 VLP, 38.7 ± 11.9 placebo	52 LI, 50 VLP, 52 placebo
Peselow et al., 1980	48 weeks	(1) LI, n = 21 (2) Placebo, n = 12	(1,2) NA	(1,2) NA	BD	Mood status not defined	34.9 (10.7) LI, 39.8 (12.0) placebo	NA

APT: adjunctive personalized treatment (could not receive any adjunctive atypical antipsychotic drug), APZ: aripiprazole, LI: lithium, LTG: lamotrigine, NA: not available, OLZ: olanzapine, QTP: quetiapine, RSP: Risperidone, VLF: Venlafaxine, VLP: Valproate sodium or divalproex.

3.5. Quality of studies and risk of Bias

As shown in Table 2, most studies were rated as high quality (low risk category) according to the Cochrane Collaboration Risk of Bias tool 2.0 (RoB), with just one study (Peselow et al., 1980) rated as medium-low quality (medium-high risk of bias category).

4. Discussion

4.1. Summary of evidence

To our knowledge, this is the first systematic review and meta-analysis to investigate the impact of lithium treatment on weight gain in BD. We systematically reviewed 20 studies that compared weight change with lithium and its comparators. Subsequently, our meta-analysis on a subset of these studies suggests that weight gain with lithium is not significant, notwithstanding a trend to weight increase of less than 0.5 Kg, with greater weight gain in shorter studies. Weight gain with lithium was significantly lower than with active comparators. Finally, overall baseline-to-endpoint weight gain differences between lithium and placebo were not significant.

The parsimonious conclusion is that weight gain with lithium treatment is far less significant than previously thought. A further possible explanation for this lack of statistically significant differences in weight gain with lithium or between lithium and placebo, could be the increased risk of being overweight related to BD itself, possibly associated to genetic factors or lifestyle habits (Keck and McElroy, 2003). Patients with BD appear to be at greater risk than the general population for overweight and obesity (Keck and McElroy, 2003; Tully et al., 2020; Fagioli et al., 2008). This seems to be related, beyond treatment with medications associated with weight gain, alone or in combination, to factors including comorbid binge-eating disorder, the number of

depressive episodes, greater propensity to atypical depressive symptoms with increased appetite (Mitchell et al., 2001), excessive carbohydrate consumption, and low rates of exercise (Wildes et al., 2006; Shah et al., 2006). The greater weight gain in shorter studies could be due to initial fluid retention that stabilizes with time, it is also possible that people who have more weight gain early on are more likely to drop out. Moreover a shorter duration of illness may be associated with higher weight gain possibly because the receiving patients have not yet achieved sustained remission, thus requiring polypharmacy; one other explanation could be that patients may have not yet taken full advantage of psychoeducation intervention to enhance dietary habits and reduce the overall number of medications besides the cornerstone treatment represented by lithium. (Fornaro et al., 2016). Regarding the greater weight gain with the active comparators, this is in line with the evidence of an important impact in weight gain of different pharmacologic options for BD (Torrent et al., 2008). It should be noted that some included studies compared lithium to treatment alternatives known for their low metabolic impact, such as lamotrigine (Grootens et al., 2018), which may influence these results (Calabrese et al., 2003; Bowden et al., 2003).

Considering the systematic review, only one study reported that lithium was associated with more weight gain than placebo, while 6 studies found no significant differences in weight gain between lithium and placebo. Furthermore, three studies with venlafaxine and lamotrigine as active comparators reported greater weight gain with lithium than with active comparators, while four studies using aripiprazole, lamotrigine and valproic acid as active comparators found no significant difference compared to lithium. Finally, eight studies showed greater weight gain with the active comparator than with lithium; these used atypical antipsychotics (quetiapine, olanzapine, and risperidone) and valproate as active comparators. These agents are known to increase body weight.

This data is mostly in line with the literature, where weight gain with

Table 3
Weight outcomes and quality of included studies.

First author and publication year	Definition of weight gain	Outcomes relating to weight gain	Study quality
Studies entering the meta-analysis			
Yaramala et al., 2020	(a) mean (SD) weight gain kg	(a) LI, 1.8 (3.5); placebo, 1.7 (4.1). NS	High
Findling et al., 2019	(a) mean (SD) weight change kg (b) mean (SD) BMI change kg/m ²	(a) LI, -1.6 (3.6); QTP, 1.2 (3.7). (b) LI, -0.6 (1.4); QTP, 0.6 (1.4). NS, despite small decreases in (a) and (b) in LI group.	High
Gao et al., 2018	(a) patients with >7% weight increase from baseline (b) body weight LS-mean (SE) at 2,6, 8, 12, 16, 20, 24 weeks (c) BMI kg/m ² LS-mean (SE) at 2,6, 8, 12, 16, 20, 24 weeks	(a) at 24 weeks occurred in 21 (8.8 %) subjects treated with QTP + APT and 29 (12.3 %) of those treated with LI + APT (p = 0.8). (b),(c) QTP and LI based pharmacotherapy produced modest but significant increases in body weight and BMI regardless of binge-eating status. QTP + APT group experienced greater increases in (b) y (c) than LI + APT. Significant increases in (b) y (c) at all time points in QTP + APT group, but only at 20 and 24 weeks in the LI + APT group.	High
Amsterdam et al., 2016	(a) mean (SD) weight gain, [range] observed kg (b) mean (SE) weight gain, [95 % CI] predicted kg	(a) LI, -0.24 (2.49), [-7.26 to 5.90]; VLF -1.31 (3.85), [-14.97 to 9.98]. (b) LI, 0.37 (0.31), [0.24 to 0.98]; VLF -1.20 (0.42), [-2.02 to -0.37]. Modest, albeit statistically significant between-group difference, small weight loss in VLF group relative to the LI group	High
Findling et al., 2015	(a) mean (SD) change in weight z score ¹ kg.	(a) LI, 0.9 (1.6); placebo 1.2 (1.7). NS	High
Geller, 2012	(a) mean (SD) weight gain kg (b) mean (SD) increase in BMI kg/m ²	(a) RSP, 3.31 (1.75) vs LI, 1.42 (1.62), p = 0.001. RSP, 3.31 (1.75) vs VLP, 1.67 (1.92), p = 0.001. In RSP group (a) was significantly greater than in LI and VLP group. (b) RSP, 1.37 (0.77) vs LI, 0.37 (1.24), p = 0.001. RSP, 1.37 (0.77) vs VLP, 0.35 (0.82), p = 0.001. In RSP group (b) was also significantly greater than in LI and VLP group.	High
Bowden et al., 2010	(a) mean weight change from baseline (analysis of variance). (b) patients with >7% weight gain from baseline	(a) LI, 0.2 (3.3); VLP, 1.1 (2.9), p = 0.04. Mean weight gain was greater in the VLP group than in the LI group. (b) LI, 9 %; VLP, 7 %, p = 0.20.	High
Keck et al., 2009	(a) mean (SE) change in weight from baseline OC (b) mean (SE) change in weight from baseline LOCF (c) mean weight change by baseline	(a) APZ (n = 40), 1.34 (0.63); LI (n = 53), 0.62 (0.55), p = 0.39. NS (b) APZ, 1.4 (0.56); LI, 0.31 (0.54), p = 0.113. NS (c) NS (d) mid-BMI subgroup (23–27 kg/m ²), LI, 0.12	High

Table 3 (continued)

First author and publication year	Definition of weight gain	Outcomes relating to weight gain	Study quality
	BMI ² OC (d) mean weight change by baseline BMI ² LOCF (e) patients with >7% weight gain from baseline OC (f) patients with >7% weight gain from baseline LOCF	(0.48); APZ 1.57 (0.50), p = 0.041. (e) APZ, 14.6 % (6/41); LI 3.7 % (2/54), p = 0.059, NS (f) NS	
Tohen et al., 2005	(a) mean (SD) weight change kg (b) patients with >7% weight increase from baseline (c) patients presenting weight increase or decrease as an adverse event	(a) OLZ, 1.8 (5.8); LI, -1.4 (5.0), p < 0.001. Significantly greater for the OLZ group than in the LI group. (b) OLZ (n = 64), 29.8 %; LI (n = 21), 9.8 %, p < 0.001. Significantly greater for the OLZ group than in the LI group. (c) weight increase: OLZ, 6.5 %; LI, 4.7 %, p = 0.53, weight decrease: OLZ, 3.2 %; LI, 5.1 %, p = 0.35.	High
Studies entering only the systematic review			
Hayes et al., 2016	(a) increase in body weight ≥ 7% from baseline (b) increase in body weight ≥ 15% from baseline	(a) and (b) significantly higher in individuals taking VLP, OLZ, or QTP compared to LI. (b) VLP HR 1.62; 95 % CI 1.31–2.01; p < 0.001; OLZ HR 1.84; 95 % CI 1.47–2.30; p < 0.001; QTP HR 1.67; 95 % CI 1.24–2.20; p < 0.001, after adjustment, rates of weight gain were higher with VLP, OLZ, and QTP than LI.	High
McIntyre et al., 2011	(a) mean weight change from baseline LOCF kg (b) mean weight change from baseline OC kg (c) patients with >7% weight gain or loss from baseline	(a) LI, 0.74; APZ, 0.97, p = 0.60. (b) LI (n = 9), 2.71; APZ (n = 7), 5.66, p = 0.46. (c) LI vs APZ, weight gain (20.0 % vs 42.9 %, p = 0.323) or weight loss (10.0 % vs 0 %, p = 0.403). Weight gain was moderate and NS, except patients with a baseline BMI < 25 kg/m ² , that showed a greater increase in mean weight with APZ.	High
Amsterdam and Shults, 2008	(a) weight gain as an adverse effect	(a) LI, 20 % (8/40); VLF, 9.3 % (4/43)	High
Niufan et al., 2008	(a) mean increase in weight kg (b) mean BMI increase kg/m ² (c) patients with >7% weight gain from baseline	(a) OLZ, 1.85; LI, 0.73, p = 0.014; (b) OLZ, 0.69; LI, 0.27, p = 0.012. (c) OLZ, 16.2 %; LI, 2.9 %, p = 0.009 Mean increases were statistically significantly higher in the OLZ treatment group. In addition, significantly more OLZ patients had a clinically significant weight increase compared to LI.	High

(continued on next page)

Table 3 (continued)

First author and publication year	Definition of weight gain	Outcomes relating to weight gain	Study quality
Bowden et al., 2008	(a) patients with >7% weight gain from baseline	(a) LI, 4 % (6/150); VLP, 8.7 % (13/149)	High
Bowden et al., 2005	(a) mean (SD) weight change LOCF and OC kg (b) patients with >7% weight increase from baseline, adjusted for baseline BMI category (c) patients presenting weight increase or decrease as an adverse event	(a) QTP, 2.6; placebo, -0.08 (LOCF). QTP, 3.3; placebo, 0.3 (OC). LI, 0.7 (LOCF); LI, 1.0 (OC). Significantly higher in QTP than placebo ($p < 0.001$). LI not significantly different from placebo. (b) BMI < 25 (placebo: 9.2 %; QTP: 33.3 %, and LI: 16.9 %) BMI ≥ 25 (placebo: 6.3 %, QTP: 24.4 %, and LI: 12.1 %). Significantly more frequent in the QTP group than in the placebo group ($p = 0.008$). Most patients who gained $\geq 7\%$ of their weight belonged to the group with baseline BMI < 25 while a smaller proportion belonged to the group with baseline BMI ≥ 25 . (c) Weight increase: LI, 6.1 %; QTP, 15 %; Placebo, 1 %. Weight decrease: LI, 6 %; QTP, 1.9 %; Placebo, 1 %.	High
Calabrese et al., 2005	(a) patients presenting weight gain as an adverse event.	(a) LI, 3 %; VLP, 4 %.	High
Calabrese et al., 2003	(a) mean weight change kg (b) patients with >7% weight increase from baseline	(a) placebo, 1.2; LI, 4.2; LTG, -2.2 (LTG vs LI: $p < 0.1$; comparisons with placebo were not significant). (b) placebo, 6 %; LI, 10 %; LTG, 7 %.	High
Bowden et al., 2003	(a) patients with >7% weight increase from baseline	(a) LTG, 11 %; LI, 10 %; placebo, 2 %.	High
Bowden et al., 2000	(a) patients presenting weight increase as an adverse event	(a) LI, 13 %; VLP, 21 %; placebo, 7 %. VLP > placebo, $p < 0.004$. Significantly higher incidence of tremor and weight gain in VLP than in the placebo group.	High
Peselow et al., 1980	(a) average (SD) weekly and cumulative weight change from baseline	(a) LI, 3.97 (2.81) kg; placebo, 1.06 (1.49), $p < 0.01$. Statistically significant between-group difference.	Medium-low

APT: adjunctive personalized treatment (could not receive any adjunctive atypical antipsychotic drug), APZ: aripiprazole, BMI: body mass index, LI: lithium, LOCF: last observation carried forward, LS: least squares, LTG: lamotrigine, NS: No statistically significant between-group difference, OC: observed cases, OLZ: olanzapine, QTP: quetiapine, RSP: Risperidone, VLP: Venlafaxine, VLP: Valproate sodium or divalproex. 1. Change score is the week value minus the baseline value; baseline is defined as the first visit of the efficacy phase mean $\pm$ SD, 2. BMI baseline category: <23 kg/m², 23–27 kg/m² or >27 kg/m².

some second generation antipsychotics like quetiapine, risperidone, and olanzapine (Kim et al., 2008; Huhn et al., 2019; Bak et al., 2014) as well as with valproate (Grootens et al., 2018) is well established. In contrast, aripiprazole (Bak et al., 2014) and lamotrigine (Grootens et al., 2018; Sachs et al., 2006) have a more neutral metabolic profile, and in some

studies, they were even associated with weight loss (Bowden et al., 2006), although with aripiprazole, data are inconsistent in other disorders and in pediatric populations (Schoemakers et al., 2019). Finally, venlafaxine appears to be associated with weight loss (Kraus et al., 2002; de Oliveira et al., 2004). Nevertheless avoiding concurrent prescription of antidepressant with lithium in the long-term management of bipolar depression should, in theory, minimize the impact of mood-de-stabilizers (antidepressants), thus further reducing the need for otherwise higher mean doses of lithium or complex polypharmacy with concurrent antipsychotic treatments. Polypharmacy may otherwise affect long-term weight gain in BD. Some of these results are also consistent with previous studies where obesity and overweight in BD are considered to be partly related to prescribed drugs (Torrent et al., 2008).

Although the biological mechanisms that lead to lithium-related weight gain are not entirely clear, researchers speculate that several processes are likely to be involved and different hypotheses have been proposed. These processes may work alone or in combination to cause weight gain in people on lithium therapy (Gitlin, 2016; Mangge et al., 2019).

Hypothetically, early weight gain after starting lithium therapy could lead in regaining weight that was previously lost unintentionally. Another mechanism related with weight gain could possibly result from the increased thirst caused by lithium, leading to the ingestion of high-calorie drinks (Peselow et al., 1980). Lithium might also cause sodium and water retention in people who consume a high-salt diet, which can lead to added body weight (Demers and Heninger, 1970); however, this finding is controversial. Other authors support that weight gain in lithium-treated patients is due not to an increase in fluid retention but rather to an increase in fat and other solid tissues (Peselow et al., 1980). Unrecognized hypothyroidism, leading to a reduced metabolic rate which in turn leads to weight gain may play a role in a small minority of patients (Cayköylü et al., 2002; Shine et al., 2015) considering that skilled clinicians do routinely monitor thyroid functioning and easily fix hypothyroidism in most of the cases.

However, it seems likely that, for most patients, lithium alters other core mechanisms that can cause weight gain (Ackerman and Nolan, 1998). Many studies have shown lithium to have insulin-like properties, influencing carbohydrate metabolism in a variety of ways, some of which may form the basis for the increased weight gain, while other studies have described effects in lipids metabolism (Peselow et al., 1980). The mechanisms of action implicated in lithium-induced weight gain include an increased glucose uptake into the cells through stimulation of hexokinase and pyruvate kinase and inhibition of muscle protein kinase. Valproate and lithium also feature weight gain as a side effect and both interact with HDACs (histone deacetylases), which are important enzymes for epigenetic modulation by catalyzing the deacetylation of histones. The deacetylation of histones induces a tighter wrapping of proteins around the DNA and blocks transcription by physically limiting the access of transcription factors (Gracious and Meyer, 2005).

Lithium may also have direct effects on mitochondrial energy generation both alone and in combination with other agents (Bortolasci et al., 2020; Maurer et al., 2009). In addition to insulin-like properties (Peselow et al., 1980), lithium may have direct appetite stimulating effects in the hypothalamus (Keck and McElroy, 2003). Also, recent studies associated leptin with weight gain during lithium augmentation (Bopp et al., 2019; Ricken et al., 2016).

The risk of gaining weight while taking lithium is greatest during the first two years of treatment (Gitlin, 2016) and in addition to pharmacotherapy, several factors can influence the likelihood of gaining weight while taking lithium treatment (Gitlin, 2016), including treatment duration, sex or baseline weight for example. One study evaluating mean weight change found no significant difference between placebo, aripiprazole and lithium at week 3, nor between aripiprazole and lithium at week 12 in any subgroup “adjusted by baseline BMI category” (BMI b23 kg/m², 23–27 kg/m² or N 27 kg/m²) (Keck et al., 2009).

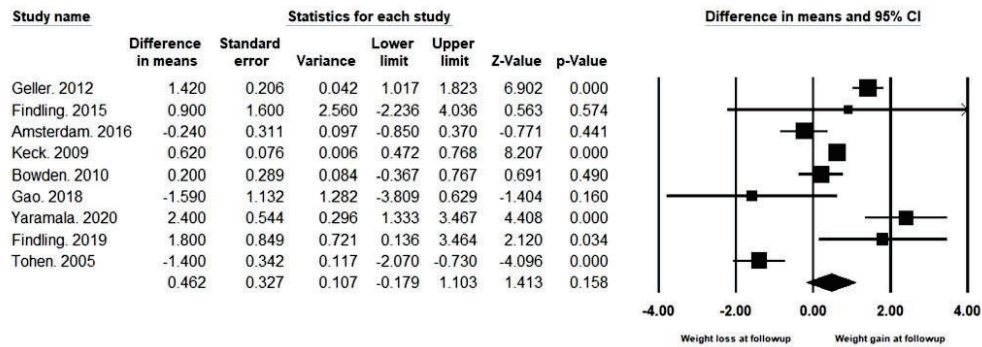


Fig. 2. Weight change during lithium treatment – Forest plots with the summary effect size (Difference in means) of weight gain, between lithium treated patients at follow up compared to baseline. Studies ordered based on trial length (small to large).

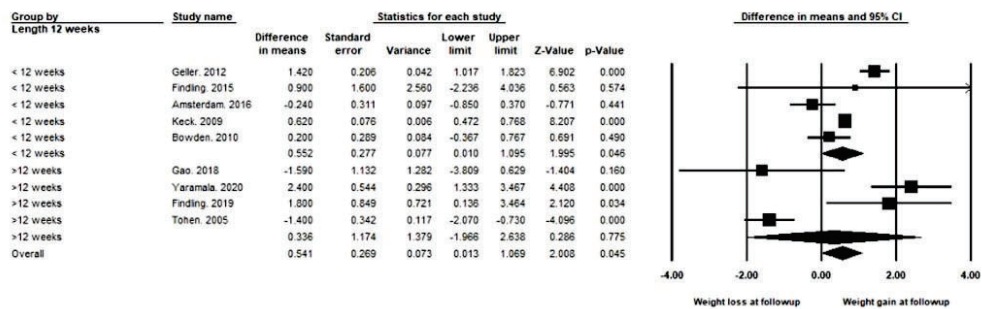


Fig. 3. Weight change during lithium treatment according trial length – Forest plots with the summary effect size (Difference in means) of weight gain, between patients treated with lithium in 2 subgroups: shorter than 12 weeks and longer than 12 weeks.

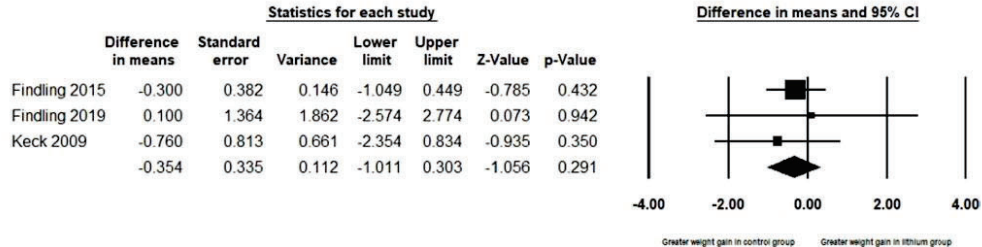


Fig. 4. Weight change in lithium treatment compared to placebo – Forest plots with the summary effect size (Difference in means) of weight gain, between patients treated with lithium versus placebo.

Another study evaluated the impact of baseline binge eating, showing that the largest increases over 24 weeks in body weight and BMI, and waist circumference in women occurred in quetiapine-treated patients with baseline binge-eating, relative to quetiapine-treated patients without binge eating and lithium-treated patients with or without baseline binge-eating (Yaramala et al., 2020). Patients with obesity showed greater weight gain while on lithium compared to patients without obesity (Bowden et al., 2006). Other studies showed that baseline body weight predicted greater weight gain (Vendsborg et al., 1976; Vestergaard et al., 1988). Finally, unhealthy lifestyle such as smoking, substance/alcohol use, poor dietary habits, and sedentary life

can also contribute to weight gain as well as to the development and severity of medical comorbidity and clinical symptoms in BD (Fagioli et al., 2008; Sylvia et al., 2013a, b).

Taken together, our results suggest an unexpectedly low impact of lithium on weight gain. This is important new data when choosing pharmacological maintenance treatment options in patients with BD. Even though weight gain with lithium did not reach statistical significance, the trend to weight increase with lithium, and particularly with other active comparators, suggests that careful monitoring of weight changes in patients before and after drug prescription should be implemented in clinical practice. Drugs which potentially cause weight

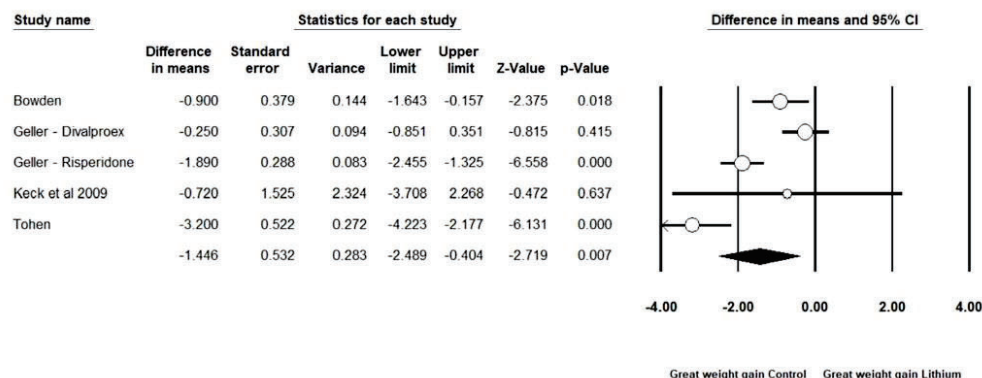


Fig. 5. Weight change in lithium treatment compared to active comparators – Forest plots with the summary effect size (Difference in means) of weight gain, between patients treated with lithium versus active comparators.

gain should be avoided, if possible, in overweight patients with BD. Furthermore, eating habits and daily activities should be targeted as they may also have a significant impact on overall health and weight-related issues (Torrent et al., 2008), as seen in the placebo groups, where independently from drug treatment, weight gain is prone to occur.

4.2. Strengths and limitations

As far as we know, our is the first systematic review and meta-analysis focusing on weight-related change with lithium treatment. Our study analyzed several weight measures across different studies by comparing weight change during lithium treatment as well as comparing weight change with placebo and/or active comparators. Thus, we were able to identify trends in weight change with lithium, placebo and active comparators that are used in drug treatment of BD.

Limitations include a generally high level of statistical heterogeneity in our meta-analyses; due to the limited studies, comprehensive subgroup analysis to detect factors that may affect heterogeneity was not feasible. Potential factors that may be affecting this between group differences are different trial durations, assessment measures used, and variable medications and dosing employed as well as a previous open label phase, in some studies, where patients could receive other treatments that were discontinued in extension phases. However, most included studies were of high quality and had a low risk of bias. Also, we were not able to meta-analyze nor perform a systematic review of the outcome on other metabolic measures such as lipid or glycemic profiles due to dearth of data. For similar reasons, we were unable to perform subgroup analysis by lithium dosage or age. Additionally, we grouped all studies together, regardless of mood state. It is possible that the participants with a depressive mood status had a different diet composition compared to a manic episode or prior to an acute episode, and this might have influenced the results. However, the included studies did not describe diet composition or lifestyle habits of the participants; thus it is not possible to say to which extent the weight gain is due to drug treatment, to lifestyle changes or pathophysiology inherent to BD itself. Moreover, a sizeable proportion of the studies could not control for other potential confounding factors, e.g., concurrent hypothyroidism induced by lithium administration, what can lead to weight gain, reducing metabolic rate as described above.

4.3. Conclusions

This is the first systematic review and meta-analysis to examine

weight change with lithium treatment in people with BD. According to our results, weight gain with lithium did not reach statistical significance and was clinically irrelevant. Weight gain was greater in shorter studies. Weight gain with lithium was significantly lower than with active comparators, with no significant differences compared to placebo. This meta-analysis can inform clinical decisions and avoid potential delay in first line treatment initiation due to potential weight gain concerns of which we found no sound evidence.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of Competing Interest

SGC has received CME-related honoraria, or consulting fees from Janssen-Cilag, Italfarmaco, Angelini and Lundbeck and reports no financial or other relationship relevant to the subject of this article.

GA has received CME-related honoraria, or consulting fees from Janssen-Cilag, Lundbeck and Angelini with no financial or other relationship relevant to the subject of this article.

EV has received grants and served as consultant, advisor or CME speaker for the following entities (unrelated to the present work): AB-Biotics, Abbvie, Angelini, Celon, Dainippon Sumitomo Pharma, Ferrer, Gedeon Richter, GH Research, Janssen, Lundbeck, Otsuka, Sage, Sanofi-Aventis, and Takeda.

IP has received CME-related honoraria, or consulting fees from ADAMED, Janssen-Cilag and Lundbeck (unrelated to the present work).

MB has been a speaker for Abbot, Astra Zeneca, Janssen and Janssen, Lundbeck and Merck and served as a consultant to Allergan, Astra Zeneca, Bioadvantex, Bionomics, Collaborative Medicinal Development, Janssen and Janssen, Lundbeck Merck, Pfizer and Servier – all unrelated to this work.

AGP has received CME-related honoraria, or consulting fees from Janssen-Cilag, Angelini and Lundbeck and reports no financial or other relationship relevant to the subject of this article.

All other authors report no biomedical financial interests or potential conflicts of interest related to the present article.

Acknowledgements

EV thanks the support of the Spanish Ministry of Science and Innovation (PI15/00283, PI18/00805) integrated into the Plan Nacional de I

+ D+I and co-financed by the ISCIII-Subdirección General de Evaluación and the Fondo Europeo de Desarrollo Regional (FEDER); the Instituto de Salud Carlos III; the CIBER de Mental Health (CIBERSAM); the Secretaria d'Universitats i Recerca del Departament d'Economia i Coneixement (2017 SGR 1365), the CERCA Programme, and the Departament de Salut de la Generalitat de Catalunya for the PERIS grant SLT006/17/00357. Thanks the support of the European Union Horizon 2020 research and innovation program (EU.3.1.1. Understanding health, wellbeing and disease: Grant No 754907 and EU.3.1.3. Treating and managing disease: Grant No 945151).

GA's research is supported by a Pons Bartran 2020 grant (PI046549). MB is supported by a NHMRC Senior Principal Research Fellowship (1156072), and has received Grant/Research Support from the NIH, Cooperative Research Centre, Simons Autism Foundation, Cancer Council of Victoria, Stanley Medical Research Foundation, Medical Benefits Fund, National Health and Medical Research Council, Medical Research Futures Fund, Beyond Blue, Rotary Health, A2 milk company, Meat and Livestock Board, Woolworths, Avant and the Harry Windsor Foundation.

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5. Discusión

Discusión general

El TB continúa siendo un trastorno de difícil manejo, con elevadas tasas de síntomas residuales e importante repercusión funcional, así como importante carga socioeconómica.(4)

Aparte de la dificultad en controlar los síntomas psiquiátricos propios de la enfermedad, en los últimos años ha surgido una preocupación creciente por la alta comorbilidad médica observada en estos pacientes, derivada de diferentes factores de riesgo, y que condiciona una reducción de la esperanza media de vida de estos pacientes, con afectación funcional, peor curso clínico y también elevados costes socioeconómicos asociados.(52)

En este sentido, cada vez hay mayor interés por investigar métodos complementarios al tratamiento habitual que permitan aliviar síntomas psiquiátricos, pero que también puedan contribuir a una mejoría de la salud física de esta población. En este contexto, hay una creciente investigación en los ámbitos de la psiquiatría nutricional y del estilo de vida, tanto en el análisis de las interrelaciones entre diferentes factores de estilo de vida con el curso de la enfermedad, como en el desarrollo de programas de intervención para su aplicación clínica.

En el TB se trata de un área novedosa, donde se empiezan a dar los primeros pasos y donde aún hay pocos estudios disponibles. En esta línea, esta tesis doctoral trata de profundizar en el conocimiento de la psiquiatría nutricional aplicada al TB, contribuyendo con información que puede resultar útil desde un punto de vista clínico, y permitir la generación de nuevas hipótesis de estudio para futuras líneas de investigación.

El primer proyecto, estudio observacional, **(estudio I)** tiene como objetivo caracterizar una muestra representativa de pacientes con TB de nuestra zona, entender las relaciones entre patrones dietéticos, ejercicio y tratamientos farmacológicos con el curso de la enfermedad y parámetros metabólicos.

El segundo proyecto, la metaanálisis, **(estudio II)** tiene como objetivo estudiar la repercusión a nivel de cambio ponderal, del litio, uno de los fármacos más utilizados para el TB, del que se disponía hasta la fecha de escasa e inconsistente información sobre su efecto a nivel de cambio de peso en estos pacientes. También pretendemos con este estudio meta analítico comparar los efectos sobre el cambio de peso entre litio, placebo y otras alternativas, ofreciendo una información aplicable a la práctica clínica diaria de terapeutas y pacientes.

Los resultados derivados de estos proyectos son pequeños pasos para entender el impacto de diferentes factores (dieta, ejercicio, tratamiento farmacológico) a nivel metabólico, así como para caracterizar y entender posibles relaciones entre patrones dietéticos y variables clínicas y metabólicas del TB, con el intuito de que puedan servir de base para nuevos estudios que profundicen en la aplicación de este conocimiento a la práctica clínica.

Seguidamente, los principales resultados serán discutidos en las respectivas secciones.

Caracterización de la población a estudio, en cuanto a hábitos de estilo de vida, parámetros clínicos y metabólicos.

Uno de los objetivos de nuestro trabajo **(estudio I)** era caracterizar una muestra representativa de nuestra población en diferentes ámbitos, y establecer las relaciones existentes entre estos factores, así como con el curso de enfermedad o tratamiento farmacológico.

Parámetros clínicos

En una gran proporción de pacientes se ha identificado una afectación funcional moderada-severa, con una calidad de vida percibida relativamente baja, aun tratándose de una muestra de pacientes eutímicos o con síntomas depresivos leves, por criterios de estudio, lo cual puede justificar parcialmente las dificultades de estos pacientes para seguir un estilo de vida adecuado, a nivel de dieta y ejercicio, aun en ausencia de episodios afectivos mayores.(91)

Parámetros metabólicos

Se ha detectado una gran proporción de pacientes en el rango de IMC considerado como obesidad ($IMC \geq 30$), en un porcentaje incluso superior al descrito en otros estudios.(57,66) Este hallazgo es especialmente relevante dado el impacto conocido del sobrepeso y obesidad sobre la salud física y mental de estos pacientes, con mayor severidad de síntomas depresivos e incluso mayor afectación cognitiva.(67,164)

La presencia de síndrome metabólico se describió en prácticamente un tercio de nuestra muestra, en línea con estudios anteriores.(75) Tal como ocurre con la presencia comórbida de obesidad, se ha observado que la coocurrencia de TB con síndrome metabólico se puede asociar a un impacto negativo sobre la salud física, con mayores tasas de mortalidad prematura, con un peor curso de enfermedad, más cronificado, peor funcionamiento global, peor calidad de vida percibida y mayores tasas de ciclación rápida.(61,165)

Hábitos de estilo de vida

En lo que se relaciona con el nivel de actividad física, casi un tercio de la muestra ha sido clasificada como poco activa físicamente, en consonancia con los estudios existentes que exhiben una elevada tendencia al sedentarismo de pacientes con TB.(116)

A nivel de adherencia a la dieta mediterránea, nuestra población de estudio mostró una baja adherencia, tal como anticipado por los estudios previos que indican una tendencia a hábitos dietéticos poco saludables.(94,111)

En este estudio, aparte de la utilización de una escala de adherencia a la dieta mediterránea, se ha empleado un recurso estadístico especialmente útil en estudios de psiquiatría nutricional, denominado análisis factorial,(166) que permite una mejor caracterización de los patrones dietéticos de la población a estudio, así como la investigación de su correlación con otros parámetros a estudio. En nuestro estudio, el análisis factorial ha permitido identificar tres patrones dietéticos principales, basados en la información dietética de los cuestionarios de frecuencia alimentaria: “vegetariano”, “omnívoro” y “Western”.

Estos resultados apoyan la importancia del enfoque de la psiquiatría nutricional, resaltando la necesidad de monitorizar variables metabólicas y explorar hábitos dietéticos y de ejercicio físico en nuestra población en la práctica clínica habitual, permitiendo detectar pacientes que se podrían beneficiar de intervenciones tanto individuales como grupales a nivel de mejoría de estilo de vida, y teniendo en consideración los condicionantes y limitaciones funcionales de estos pacientes.

Relación entre los hábitos de estilo de vida, patrones dietéticos y tratamientos farmacológicos con parámetros metabólicos y el curso de la enfermedad en pacientes con TB.

Además de la caracterización de la población en cuanto a los diferentes parámetros descritos anteriormente, nuestro trabajo pretendía estudiar las relaciones de algunos de estos factores entre sí, así como su impacto a nivel metabólico y clínico.

Hábitos de estilo de vida, patrones dietéticos y su impacto a nivel clínico y metabólico

En este trabajo se ha descrito una correlación inversa entre la cantidad de ejercicio físico realizada y los niveles de colesterol, en línea con la evidencia existente sobre el efecto beneficioso de la realización de ejercicio para la salud física y metabólica.(167) Asimismo, se ha encontrado una asociación significativa entre adherencia a dieta mediterránea y mayor calidad de vida percibida, mientras que el consumo de frutos secos se ha relacionado con mejores parámetros metabólicos de acuerdo con la literatura previa,(102) no encontrándose tal como esperado y descrito en estudios previos una correlación con síntomas depresivos,(98,103) posiblemente debido entre otros factores a un reducido tamaño muestral.

De los tres patrones dietéticos descritos en nuestra muestra, “vegetariano”, “omnívoro” y “Western”, el patrón que ha demostrado la mayoría de las relaciones estadísticamente

significativas con variables clínicas y metabólicas ha sido el patrón “vegetariano”, con un impacto positivo tanto en la salud física como mental.

La mayoría de los estudios previos se han centrado en el impacto del consumo de pescado, omega 3 o dieta mediterránea, mostrando en general una asociación inversa entre dieta saludable y síntomas depresivos.(99) A nivel de patrones dietéticos, los que habitualmente se asocian a mejor impacto sobre síntomas depresivos y se sugieren como saludables son aquellos ricos en vegetales, fruta, frutos secos, legumbres y marisco con consumo reducido de comidas ultraprocesadas y azúcares. (101,107) Dicha evidencia concuerda parcialmente con los resultados obtenidos, salvo por la ausencia de pescado o marisco en el patrón “vegetariano”, ya que, de los 3 patrones detectados, el vegetariano sería el que más se asemejaría a las recomendaciones de dieta saludable, lo cual, aun en ausencia de estudios específicos sobre dieta vegetariana en pacientes con TB, podría apoyar parcialmente los resultados obtenidos.

En relación a la dieta vegetariana en concreto, hasta nuestro conocimiento no existen estudios de asociación en pacientes con TB, mientras que en depresión se han encontrado resultados contradictorios,(168) con una evidencia más homogénea en lo que respeta al impacto en la salud física o metabólica, donde la dieta vegetariana ha mostrado de forma consistente efectos positivos, reduciendo el riesgo de problemas cardiovasculares en general,(109) en línea con nuestros resultados.

Tratamiento farmacológico y su impacto a nivel clínico y metabólico

En la muestra estudiada, los pacientes que recibían tratamiento con ácido valproico han mostrado una asociación positiva con el IMC, proporción de síndrome metabólico y niveles de triglicéridos.(50) También los pacientes en tratamiento con antipsicóticos presentaban un perímetro abdominal, IMC y niveles de triglicéridos aumentados y peor funcionamiento global, en línea con la literatura previa.(49) Finalmente, los pacientes tratados con litio presentaban una correlación negativa con los niveles de colesterol, con un perfil metabólico con tendencia más favorable en comparación a las otras alternativas estudiadas.

Tras realizar un análisis multivariado, sólo la asociación entre tratamiento con antipsicóticos, IMC y perímetro abdominal aumentado, mostró ser estadísticamente significativa independientemente de los otros tratamientos, lo que se podría deber entre otros aspectos a un pequeño tamaño muestral.

Cambio de peso en pacientes en tratamiento con litio

En la muestra estudiada (**estudio I**), como comentado previamente, aparte de la relación inversa detectada entre tratamiento con litio y niveles de colesterol, los pacientes que recibían litio mostraban tendencia a una asociación inversa con otros parámetros metabólicos como el IMC, peso, o perímetro abdominal, aunque no llegando a un grado de significación estadística.(129,130)

En el metaanálisis realizado (**estudio II**), se ha investigado más a fondo el impacto del tratamiento con litio en el aumento de peso, en pacientes con TB, siendo el primer metaanálisis sobre este tema realizado hasta nuestro conocimiento.

Cambio de peso con litio

Los resultados de nuestro trabajo (**estudio II**) sugieren que el aumento de peso relacionado con el tratamiento con litio es considerablemente inferior al previamente pensado. La tendencia al aumento de peso observada en pacientes en tratamiento con litio en nuestro estudio es relativamente baja y no es estadísticamente significativa, con un mayor aumento de peso en estudios cortos. En un estudio reciente sobre el impacto de psicofármacos en el aumento de peso, clasifican el litio como de riesgo moderado dentro de la categoría de estabilizadores del estado de ánimo,(169) aunque enfatizando la evidencia de un aumento de peso relativamente bajo, también confirmado por estudios más recientes.(129)

Aunque los mecanismos exactos que pueden conducir al aumento de peso durante el tratamiento con litio no están claros, se especula que diferentes procesos, solos o en combinación, podrían estar implicados, con diferentes hipótesis planteadas.(170,171) El aumento de peso temprano se podría deber a una ganancia de peso previamente perdido de forma intencionada. Otros mecanismos relacionados con el aumento ponderal pueden

resultar del aumento de sed producido por el litio, conduciendo a una mayor ingesta de bebidas azucaradas. El litio también puede conducir a la retención de líquido, que puede llevar a un aumento de peso extra.(172) En una minoría de casos, el hipotiroidismo no reconocido podría ser responsable de un metabolismo enlentecido y un aumento de peso subsecuente.(173)

No obstante, otros estudios proponen que en la mayoría de los pacientes el tratamiento con litio alteraría otros mecanismos relacionados con el aumento de peso. Algunos estudios exponen propiedades de tipo insulínico del litio, que influyen sobre el metabolismo de carbohidratos o inducen efectos sobre el metabolismo lipídico.(172) El tratamiento con litio también puede tener efectos directos sobre la función mitocondrial.(174,175) Finalmente, otros mecanismos relacionados con el aumento ponderal con litio son el potencial de estimular el apetito sobre el hipotálamo o la relación con leptina.(176,177)

El aumento de peso más marcado, encontrado en estudios cortos, podría estar relacionado con una retención de líquido inicial que se estabilizaría a lo largo del tiempo o que los pacientes que presenten un aumento de peso marcado tienen más tendencia a abandonar el estudio antes. También puede suceder que pacientes en estudios cortos no hayan alcanzado una adecuada estabilidad sintomática y que no se hayan beneficiado de la psicoeducación para mejorar hábitos de estilo de vida que a medio o largo plazo pueden ayudar a controlar los efectos negativos de la medicación.

El riesgo de aumento de peso es más pronunciado en los primeros años de tratamiento y además del tratamiento farmacológico hay otros factores como el sexo, peso de base o duración del tratamiento, conductas de atracones alimentarios,(178) que pueden influenciar el aumento de peso durante el tratamiento con litio. Finalmente, los factores de estilo de vida poco saludables pueden influenciar el aumento ponderal de estos pacientes.(179)

Cambio de peso con litio en comparación con alternativas terapéuticas

Asimismo, se ha encontrado que el aumento de peso con litio en comparación con otras alternativas terapéuticas ha sido significativamente inferior (**estudio II**), en línea con estudios

más recientes, que sugieren que hay más casos de aumento de peso con litio que con lamotrigina, aunque no alcanzando la significación estadística, y que claramente el litio se asociaba a menos casos reportados de aumento de peso que con algunas alternativas de mantenimiento como la olanzapina, quetiapina o valproato.(129) Estos hallazgos están en consonancia con los resultados descritos en nuestro estudio observacional, en que se sugiere un perfil metabólico más favorable con litio que con otros comparadores **(Estudio I)**.

El aumento de peso más pronunciado con comparadores activos que con el litio está en sintonía con estudios previos que evidencian un importante impacto del tratamiento con determinados fármacos sobre el aumento de peso.(180) Los estudios en que se encontró un aumento de peso estadísticamente significativo con el comparador activo en comparación con litio incluían diferentes antipsicóticos de segunda generación (quetiapina, olanzapina y risperidona)(127) y valproato.(50) Aun así, es importante tener en cuenta que, también en línea con la evidencia previa, en tres estudios incluidos en la revisión sistemática, los comparadores mostraron menor aumento de peso que el tratamiento con litio, entre ellos venlafaxina y lamotrigina (aunque en la metaanálisis venlafaxina no se consideró un comparador activo ya que no está recomendado como tratamiento de mantenimiento en monoterapia).(50,181) Finalmente, cuatro estudios en que se utilizaba aripiprazol, lamotrigina y ácido valproico no encontraron diferencias significativas en el aumento de peso en comparación con el litio; en este caso, tanto lamotrigina como aripiprazol tienen descrito un perfil más neutral en consonancia con estos resultados.(50,128)

Cambio de peso con litio en comparación con placebo

Finalmente, la diferencia de aumento ponderal entre pacientes en tratamiento con litio comparados con pacientes en tratamiento con placebo no fue estadísticamente significativa.

El hecho de que no se encuentren diferencias estadísticamente significativas en la tendencia al aumento de peso observada entre pacientes tratados con litio y placebo podría residir en la predisposición a sobrepeso relacionada con el TB en sí mismo, posiblemente derivada de factores de predisposición genética, factores de la propia enfermedad como síntomas atípicos como el aumento de apetito, o la presencia de hábitos de estilo de vida poco saludables tanto

a nivel dietético como de ejercicio físico,(66) en línea con lo descrito en el estudio de caracterización de nuestra población (**estudio I**). También el aumento de peso en pacientes “drug naive” está reportado en estudios previos y podría dar soporte adicional a este hallazgo.(53)

Así, cada vez se hace más evidente la importancia de la monitorización del aumento de peso y parámetros metabólicos en pacientes con TB en general, tanto tratados con litio, con otras alternativas o incluso en ausencia de tratamiento farmacológico.(129) Esto también resalta la importancia de diseñar programas y medidas de educación sobre hábitos de estilo de vida, que minimicen efectos secundarios, lo cual puede conducir a una mejor adherencia terapéutica y en última instancia mejor control y pronóstico tanto a nivel psiquiátrico como de salud física.

Limitaciones y fortalezas

A nivel de sus limitaciones, el **estudio I** es un estudio transversal sin seguimiento longitudinal ni grupo control, y las escalas utilizadas para evaluar dieta y ejercicio son autoadministradas, sin otras medidas objetivas de dieta o ejercicio. El tamaño muestral reducido es otra limitación importante a tener en cuenta ya que limita el poder estadístico, la utilización de múltiples comparaciones hace que los datos deben ser interpretados como exploratorios y el tratamiento farmacológico también puede ser un factor de confusión a tener en cuenta. Es importante tener en cuenta que en este trabajo los patrones dietéticos estudiados han sido obtenidos a través de un método estadístico, análisis factorial, donde se derivan diferentes patrones de la información contenida en los cuestionarios de frecuencia alimentaria. Así estudiar las implicaciones clínicas y metabólicas de nuestro patrón “vegetariano” derivado por análisis factorial, o las mismas implicaciones en pacientes que siguen una dieta vegetariana, no es comparable. Las relaciones presentadas entre los diferentes patrones dietéticos y curso de enfermedad o parámetros metabólicos no deben ser consideradas como causales al tratarse de un estudio transversal, considerando que las asociaciones obtenidas de un estudio transversal no significan necesariamente causalidad.

En relación con el metaanálisis realizado en el **estudio II** se puede identificar como principal limitación un nivel alto nivel de heterogeneidad estadística. Algunos factores potenciales que pueden justificar estas diferencias entre grupos son la duración de los ensayos, las medidas de evaluación utilizadas, la variabilidad en los tratamientos y dosis empleadas, así como una fase inicial, donde los pacientes podían recibir otros tratamientos que se discontinuaron en las fases de extensión. Por escasez de datos no se ha podido llevar a cabo un análisis por subgrupos de otras medidas metabólicas específicas, dosis de litio, edad o estado anímico. Finalmente, no ha sido posible dada la ausencia de información detallada controlar por otros factores de confusión como el tipo de dieta o la presencia de hipotiroidismo entre otros.

No obstante, nuestro trabajo tiene varias fortalezas. Hasta nuestro conocimiento el **estudio I** ha sido el primero estudio que evalúa de forma conjunta factores de estilo de vida, prevalencia de síndrome metabólico y su correlación con el curso de la enfermedad y tratamiento farmacológico, algo crucial dado que estos varios factores operan conjuntamente e interactúan entre ellos. Asimismo, se trata del primero estudio en España que evalúa patrones dietéticos según análisis factorial, y sus relaciones con diferentes parámetros en el TB, lo que es especialmente relevante dadas las marcadas diferencias en perfiles dietéticos entre países. Usar patrones dietéticos en lugar de sólo alimentos o dietas concretas permite alcanzar un conocimiento más profundo de los hábitos dietéticos y un análisis más específico de su impacto.

Otra fortaleza de esta tesis es que incluye el primer metaanálisis realizado hasta su fecha, enfocado a investigar el impacto del tratamiento con litio en el aumento de peso en pacientes con TB (**estudio II**). Esto es de especial relevancia dado que es uno de los tratamientos con mayor evidencia en cuanto a eficacia en el TB, y es prescrito en menor medida de la que sería esperable en gran parte por el temor a efectos secundarios. Por ello, este trabajo permite informar clínicos y pacientes, contribuyendo a una toma de decisión informada. Asimismo, también se han podido analizar las diferencias en el aumento de peso entre litio y placebo o comparadores activos. Los resultados derivados de la comparación con placebo y comparadores activos no sólo apoyan el perfil favorable del litio, ya previamente sugerido en el **estudio I**, sino que también insinúan la predisposición de los pacientes con TB al aumento

de peso, en ausencia de tratamiento farmacológico, posiblemente mediada por los factores de estilo de vida estudiados en el **estudio I**.

Implicaciones clínicas

De los resultados obtenidos en esta tese derivan diferentes implicaciones clínicas. El **estudio I** que, en línea con la evidencia existente, confirma en nuestra población concreta una elevada prevalencia de obesidad y síndrome metabólico, resalta la importancia de establecer protocolos más estrictos de monitorización de salud metabólica, permitiendo identificar pacientes que se pueden beneficiar un abordaje en este sentido. La detección de un nivel de funcionamiento global considerablemente afectado implica que las estrategias a desarrollar y aplicar en esta población han de ser adaptadas a las dificultades y necesidades concretas teniendo en cuenta estas dificultades de funcionamiento. Finalmente, las asociaciones positivas tanto de la adherencia a dieta mediterránea, frutos secos o el patrón “vegetariano”, así como de la realización de ejercicio y la escasa adherencia de nuestra población a estos hábitos saludables, reafirman la importancia y necesidad de desarrollar e implementar programas de intervención a nivel ambulatorio para una atención integral al paciente con TB, en conjunto con el tratamiento farmacológico y psicoterapéutico, donde se trabajen hábitos de estilo de vida para mejorar el curso de la enfermedad psiquiátrica, la salud física e incluso la adherencia al tratamiento. Sería relevante considerar el potencial control de ciertos efectos secundarios como el aumento de peso, lo cual tendría un impacto positivo en la adherencia terapéutica y en la sensación de empoderamiento y control sobre la salud en los individuos con TB. Esto también va en línea con la hipótesis de “kindling” e importancia de otros factores e intervención sobre ellos para cambiar la evolución de la enfermedad,(9) en un abordaje integrativo.(144)

En el **estudio II** nuestros resultados muestran un impacto relativamente bajo del tratamiento con litio sobre el aumento ponderal, inferior al esperado. A nivel clínico, este conocimiento puede ser crucial ya que el litio es un fármaco actualmente infrautilizado aún siendo conocido su efecto beneficioso sobre el TB, en muchas ocasiones por temor tanto de los pacientes como de los prescriptores a efectos secundarios, y estando el temor a aumento de peso entre las principales preocupaciones de los pacientes con TB antes de recibir tratamiento con este

fármaco. Este conocimiento puede ayudar a guiar en la elección de tratamiento en pacientes con varios factores predisponentes a aumento ponderal. Asimismo, y aunque no llegando a un nivel de evidencia estadístico la discreta tendencia al aumento de peso con litio, resalta la importancia de la monitorización del peso y otras medidas metabólicas en estos pacientes, integrada en la práctica clínica habitual, ya sugerida en el **estudio I**, previamente y durante el periodo de tratamiento. En este sentido, los tratamientos con mayor riesgo de aumento de peso deberían ser evitados en pacientes con factores predisponentes a aumento de peso ya conocidos. Finalmente, la implementación de medidas de educación sobre hábitos dietéticos y de ejercicio es de una importancia crucial, dado el aumento de peso observado incluso en los grupos de pacientes tratados con placebo.

Futuras líneas de investigación

Estos datos podrían abrir la puerta a nuevas hipótesis de investigación. Se deberían llevar a cabo ensayos clínicos aleatorizados a gran escala para confirmar la asociación entre una dieta vegetariana de alta calidad, con un menor riesgo de depresión y una mejor salud metabólica en pacientes con TB de acuerdo con los resultados del **estudio I**, ya que éste es el primero estudio que investiga el potencial impacto de una dieta vegetariana en el TB. Asimismo, la replicación de estudios utilizando análisis factorial de pacientes con TB podría ser interesante para detectar diferencias geográficas investigando el impacto sobre el TB en los diferentes ámbitos.

Tal como se ha demostrado en el **estudio II**, el litio presenta un impacto metabólico más favorable que otras alternativas, aunque la tendencia al aumento de peso tanto en estos pacientes como en los pacientes que reciben tratamiento con placebo hacen que sea de crucial importancia desarrollar programas de intervención para pacientes con TB, que demuestran independientemente del tratamiento farmacológico ser más proclives al aumento de peso.

Todo ello, en conjunto con la información obtenida en el **estudio I** que sugiere un impacto positivo de algunos factores dietéticos y de ejercicio, hace que el desarrollo de programas de intervención aplicados a la práctica clínica donde se trabajen hábitos de estilo de vida sea

imprescindible para mejorar el curso de la enfermedad psiquiátrica, la salud física e incluso la adherencia al tratamiento, por lo que una futura línea de investigación debería incluir ensayos controlados sobre programas de intervención en estilo de vida, en nuestra población específica, en consonancia con proyectos ya desarrollados en otros países.(182)

El perfil metabólico más favorable observado con litio que con otros comparadores tanto en el **estudio I** como en el **estudio II**, y la relación propuesta en otros estudios de este impacto más favorable con su impacto en la función mitocondrial, reafirma la importancia de líneas de investigación recientes que empiezan a surgir sobre la importancia de la función mitocondrial en el TB,(12,153) que puede funcionar de enlace entre los efectos positivos de la dieta, ejercicio o litio, en el TB y que en un futuro puede ser una diana de intervención, así como ayudar a comprender mejor diferentes perfiles de pacientes y sus necesidades específicas.(12)

6. Conclusiones

1. En nuestra población se ha evidenciado una elevada prevalencia tanto de síndrome metabólico como de obesidad.
2. La adherencia a la dieta mediterránea ha sido baja, tal como la adherencia a ejercicio físico, con una gran proporción de pacientes clasificados como físicamente inactivos en la muestra analizada.
3. La adherencia a la dieta mediterránea se ha asociado a una mayor calidad de vida percibida, mientras que la cantidad de ejercicio físico se ha relacionado inversamente con los niveles de colesterol.
4. El consumo de nueces ha mostrado asociaciones positivas a nivel de salud metabólica, mientras que el patrón de dieta vegetariana se ha asociado a un impacto positivo tanto en variables psiquiátricas como metabólicas en nuestro estudio.
5. Pacientes en tratamiento con litio han presentado un perfil metabólico más favorable que los pacientes en tratamiento con ácido valproico o antipsicóticos.
6. El tratamiento con litio no se ha asociado de forma estadísticamente significativa con el aumento de peso, aunque se ha identificado una tendencia a un aumento de peso poco relevante, más marcada en estudios cortos.
7. En comparación con litio, los comparadores activos estudiados han mostrado un mayor aumento de peso, estadísticamente significativo.
8. Pacientes tratados con placebo han presentado también tendencia al aumento de peso, sin alcanzar la significación estadística y sin diferencias estadísticamente significativas en comparación con el litio, resaltando la predisposición al aumento de peso posiblemente

relacionada con el TB y algunos de sus factores asociados, tanto biológicos como de estilo de vida.

9. Estos resultados pueden tener un impacto a nivel clínico proporcionando información relevante a la hora de toma de decisiones sobre el tratamiento farmacológico con litio, en pacientes con TB teniendo en cuenta su perfil metabólico, y evitando el retraso en la utilización de litio como primera línea por temor al aumento ponderal.
10. En conjunto, ambos estudios resaltan la importancia de un abordaje integral de estos pacientes, con una monitorización regular de variables metabólicas, e intervenciones sobre estilo de vida, dirigidas a mejorar la salud mental, física, adherencia a tratamiento y calidad de vida percibida por los pacientes.
11. Finalmente, se abren nuevas líneas de investigación, como el diseño de programas de intervención sobre estilo de vida en pacientes con TB que se puedan aplicar en ensayos controlados, así como estudios controlados que prueben la hipótesis del impacto positivo global de la dieta vegetariana en pacientes con TB, tanto a nivel metabólico como psiquiátrico.

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