TESIS DOCTORAL

EVOLUCIÓN METABOLICA Y ESTILO DE VIDA EN UNA COHORTE DE PACIENTES CON ESQUIZOFRENIA EN TRATAMIENTO CON CLOZAPINA

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Título de la tesis

EVOLUCIÓN METABOLICA Y ESTILO DE VIDA EN UNA COHORTE DE PACIENTES CON ESQUIZOFRENIA EN TRATAMIENTO CON CLOZAPINA

Memoria presentada por Andrea Mallorqui Molina para optar al grado de doctor/a por la Universitat Jaume I

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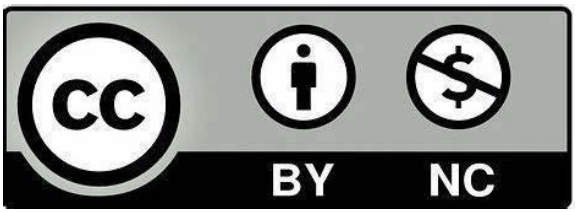

“Lo que con mucho trabajo se obtiene, más se ama.”

Aristóteles

Artículo 1

Nurse-led lifestyle intervencion in a cohort of schizophrenia pacients treated with clozapine.

Autores: Andrea Mallorqui, Cristina Oliveira, Jose Rios, María Pilar Isla-Pera, Joaquín Gil Badenes, Silvia Amoretti, Miguel Bernardo, Eduard Vieta, Eduard Parellada, Marina Garriga, Clemente García-Rizo.

2023 Oct: 46:51-57.
Doi: 10.1016/j.apnu.2023.06.008. Epub 2023 Jul 4. Factor de impacto: 2.3. Cuartil: Q2.

Artículo 2

Food craving and consumption evolution in patients starting treatment with clozapine.

Autores: Marina garriga, Andrea Mallorqui, Lourdes Serrano, José Ríos, Manel Salamero, Eduard Parellada, Marta Gómez –Ramiro, Cristina Oliveira, Eduard Vieta, Miquel Bernardo, Clemente García-Rizo.
Psychopharmacology 2019 Nov; 236(11):3317-3327.
Doi: 10.1007/s00213-019-05291-3. Factor impacto: 3.4. Cuartil: Q1.

Artículo 3

Antipsychotic–Associated Weight Gain and clinical Improvement Under Clozapine Treatment.

Autores: Marina Garriga, Andrea Mallorqui, Sonia Bernad, Victoria Ruiz-Cortes, Cristina Oliveira, Silvia Amoretti, Gisela Mezquida, Miquel Bioque, Oriol Molina, Marta Gómez-Ramiro, Eduard Vieta, Miquel Bernardo, Eduard Parellada, Clemente García-Rizo.

Jounal Clinical Psychopharmacology. 2022 Jan-Feb; 42(1):75-80.
Doi: 10.1097/JCP.0000000000001483. Factor de impacto: 2.9. Cuartil: Q2.

- Aquesta tesi disposa de l'acceptació dels coautors de les publicacions que la doctoranda presenta com a tesi i la renúncia expressa d'aquests a presentar-les com a part d'una altra tesi doctoral.

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Este proyecto empezó a gestarse hace años, casi sin darme cuenta. Empezó cuando trabajaba en Hospital de Día de psiquiatría de adultos, donde realizaba grupos de intervención de educación para la salud centrados en alimentación saludable a personas con Trastorno Mental Grave. Un buen día, el Dr. Clemente Garcia-Rizo y su compañera la Dra. Marina Garriga, me animaron a formar parte de un proyecto de investigación en el que ellos estaban. Y a raíz de ahí, nos planteamos poder tirar adelante esta tesis doctoral. En el camino han pasado muchas cosas, algunas maravillosas, como haber podido cumplir mi sueño de ser madre y otras, no tan buenas, de hecho, hubo un tiempo en que, si no llega a ser por Dr. García y su manera de alentarme a seguir adelante, hoy esta tesis doctoral no sería una realidad.

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Entidad de realización: Institut d'Investigacions Biomèdiques August Pi i Sunyer.

Tipo de entidad: Centro de I+D

Ciudad entidad realización: Barcelona, Cataluña, España

Nombres investigadores principales (IP, Co-IP,...): Carlos Clemente García Rizo; Cristina Villares Oliveira; Marina Garriga Carrizosa; Gisela Mesquida Mateos; Andrea Mallorqui Molina; Lourdes Serrano Pariente

Nº de investigadores/as: 5

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PUBLICACIONES

1. Food craving and consumption evolution in patients starting treatment with clozapine. Psychopharmacolo gy (Berl). 2019 Jun 13. doi: 10.1007/s00213-019-05291-3. PMID: 31197435. Tipo de producción: Artículo científico. Marina Garriga, Andrea Mallorquí, Lourdes Serrano, José Ríos, Manel Salamero, Eduard Parellada, Marta Gómez-Ramiro, Cristina Oliveira, Silvia Amoretti, Eduard Vieta,Miquel Bernardo, Clemente García-Rizo.

2. BMI evolution and impaired oGTT in a sample of psychotic resistant patients that starting clozapine. European Neuropsychopharmacology, Volu me 29, Supplement 1, 2019, Pages S537-S538, ISSN 0924-977X, https://doi.org/10.1016/j.euroneuro.2018.11.796 Tipo de producción: Artículo científico. Marina Garriga, Andrea Mallorqui, Merce Brat, Eva Solé, Iria Grande, Silvia Amoretti, Eduard Vieta, Clemente Garcia, Miguel Bernando.

3. Food craving evolution in schizophrenic patients starting treatment with clozapine. European Neuropsycho pharmacology. Volume 27, Supplement 4, 2017, Page S945, ISSN 0924-977X, https://doi.org/10.1016/S0924-977X(17)31673-5. Tipo de producción: Artículo científico. MarinaGarriga, Andrea Mallorquí , Lourdes Serrano , José Ríos , Manel Salamero , Eduard Parellada , Marta Gómez-Ramiro , Cristina Oliveira , Silvia Amoretti , Eduard Vieta , Miquel Bernardo, Clemente García- Rizo.

4. Assessing emotional health needs of patients with schizophrenia in order to apply more effective therapies to improve their quality of life. Assessing emotional health needs of patients with schizophrenia in order t o apply more effective therapies to improve their quality of life. BMC Nurs. 2015 Oct 8;14(Suppl 1):S3. doi: 10.1186/1472-6955-14-S1-S3. PMCID: PMC4610020. Tipo de producción: Reseña Tipo de soporte: Revista. Andrea Mallorqui Molina, Mercè Comas Forastero.

5. Antipsychotic-induced weight gain and birth weight in psychosis: A fetal programming model. J Psychiatr Res. 2019 Aug; 115:29-35. Doi: 10.1016/j.jpsychires.2019.05.004. Epub 2019 May 4.PMID: 31085376 Clinical Trial. Tipo de producción: artículo científico. Marina Garriga , Emilio Fernandez-Egea ,Andrea Mallorqui , Lourdes Serrano , Cristina Oliveira , Eduard Parellada , Brian Kirkpatrick , Eduard Vieta , Miquel Bernardo , Clemente Garcia-Rizo.

6. Antipsychotic-Associated Weight Gain and Clinical Improvement Under Clozapine Treatment. 2022 Jan-Feb;42(1):75-8. doi: 10.1097/JCP.0000000000001483. J Clin Psychopharmacol. Tipo de producción: artículo científico. Marina Garriga, Andrea Mallorquí , Sonia Bernad , Victoria Ruiz-Cortes , Cristina Oliveira , Silvia Amoretti, Gisela Mezquida, Miquel Bioque, Oriol Molina , Marta Gómez-Ramiro, Eduard Vieta, Miquel Bernardo, Eduard Parellada, Clemente García-Rizo

7. Nurse-led lifestyle intervention in a cohort of schizophrenia patients treated with clozapine Arch Psychiatr Nurs.2023 Oct;46:51-57. doi:10.1016/j.apnu.2023.06.008. Epub 2023 Jul 4.PMID: 37813503. Tipo de producción: artículo científico. AndreaMallorquí , Cristina Oliveira , Jose Rios, Maria Pilar Isla-Pera, Joaquin Gil-Badenes , SilviaAmoretti, Miguel Bernardo, Eduard Vieta, Eduard Parellada, Marina Garriga, Clemente García Rizo.

TRABAJOS PRESENTADOS EN CONGRESOS NACIONALES E INTERNACIONALES

- Título del trabajo: Antipsychotic-induced weight gain and weight at birth in psychosis: a test for the thrifty psychiatric phenotype (póster).

Nombre del congreso: SIRS Schizophrenia International Research Society.

Autores: Clemente García Rizo, Marina Garriga, Andrea Mallorqui, Lourdes Serrano, Cristina Oliveira, Eduard Vieta, Miquel Bernardo.

Ciudad de celebración: Florencia, Italia

Fecha de celebración: 4/04/2018

- Título del trabajo: Food craving evolution in schizophrenic patients starting treatment with clozapine (póster).

Nombre del congreso: 30th ECNP Congress.

Autores: Garriga, M.*, Mallorqui, A., Serrano, L., Salamero, M., Vieta, E., Bernardo, M., Garcia-Rizo, C.

Ciudad de celebración: París, Francia

Fecha de celebración: 02/09/2017

- Título del trabajo: Weight gain and gut hormones in patients initiating clozapine (póster).

Nombre del congreso: 13th World Congress of Biological Psychiatry

Autores: Clemente, García Rizo, Andrea Mallorqui, Lourdes Serrano, Cristina Oliveira, Eduard Vieta, Miquel Bernardo.

Ciudad de celebración: Cophenague, Dinamarca

Fecha de celebración: 19/06/2017

- Título del trabajo: Apetencia por "alimentos antojo" en pacientes con diagnóstico de Trastorno Mental Severo que inician tratamiento con clozapina (póster).

Nombre del congreso: XXXIV Congreso nacional de enfermería de salud mental
Autores: Andrea Mallorqui; Lourdes Serrano; Marina Garriga; Miguel Bernardo;
Clemente García Rizo.

Ciudad de celebración: Murcia, Región de Murcia, España

Fecha de celebración: 05/04/2017

- Título del trabajo: Indice de massa corporal verus perimetro abdominal como marcador del incremento de peso por antipsicóticos.

Nombre del congreso: XXXIV Congreso Nacional de Enfermería de Salud Mental.

Autores: Andrea Mallorqui; Lourdes Serrano; Marina Garriga; Miguel Bernardo;

Clemente García Rizo.

Ciudad de celebración: Murcia, Región de Murcia, España

Fecha de celebración: 05/04/2017

- Título del trabajo: Incremento de peso asociado al uso de clozapina y variación de neurohormonas intestinales.

Nombre del congreso: XIX Congreso nacional de Psiquiatria.

Autores: Clemente Garcia Rizo; Marina Garriga Carrizosa; Andrea Mallorqui molina; Cristina Oliveira; Miguel Salamero; Eduard Vieta; Miguel Bernardo arroyo.

Ciudad de celebración: Palma de Mallorca, Illes Balears, España

Fecha de celebración: 27/10/2016

- Título del trabajo: La voz de la esquizofrenia. Barreras para la salud física.

Nombre del congreso: VII Congreso Iberoamericano de Investigación Cualitativa en Salud.

Autores: Andrea Mallorqui Molina.

Ciudad de celebración: Barcelona, Cataluña, España

Fecha de celebración: 07/09/2016

- Título del trabajo: Intra_abdominal Fat gain in patients Initiating yreayment with clozapine.

Nombre del congreso: Schizophrenia International Research Society

Autores: Marina Garriga Carrizosa; Lourdes Serrano Pariente; Andrea Mallorqui Molina; Angela Torras; Cristina Oliveira; Miguel Bernardo Arroyo; Clemente Garcia Rizo.

Ciudad de celebración: Florence, Italia

Fecha de celebración: 14/04/2016

- Título del trabajo: Variables clínicas y sociodemográficas del incremento ponderal en pacientes que inician clozapina.

Nombre del congreso: XXXIII Congreso de la Asociación Nacional de Enfermería de Salud Mental.

Atuores: Andrea Mallorqui Molina; Lourdes Serrano Pariente; Angela Torres Farres; Miguel Bernardo Arroyo; Carlos Clemente García Rizo.

Ciudad de celebración: Cádiz, Andalucía, España

Fecha de celebración: 16/03/2016

- Título del trabajo: Assessing emotional Health needs ofpatients with schizophrenia in order to apply more effective therapies to improve their quality of life.

Nombre del congreso: The European academy of nursing science conference summer school

Autores: Andrea Mallorqui Molina, Merce Comes.

Ciudad de celebración: Barcelona, Cataluña, España

Fecha de celebración: 08/07/2015

- Titulo del trabajo: Clozapine placental passage at delivery: an update.

Nombre del congreso: 30th European Congress of Psychiatry.

Autores: Maria Luisa Imaz, Sara Lera, Ester Roda, Alba Roca, Anna Torres, Eva Solé, Susana Andres, Andrea Mallorquí, Lluisa Garcia-Esteve.

Ciudad de celebración: Budapest (Hungria)

Fecha de celebración: 4-7 June 2022

- Título del trabajo: Estrategies per elaborar un Projecte en el Marc Europeu.

Nombre del Congreso: Jornada de Reconeixement a la Recerca Infermera.

Autores: Andrea Mallorqui Molina

Ciudad de celebración: Barcelona (España)

Fecha de celebración: 13 maig 2022

- Titulo del trabajo: Birth weight, leptin and adiponectin in patients initiating clozapine.

Nombre del Congreso: EPA2024-ABS-3147

Autores: Lidia Ilzarbe, Marina Garriga, Cristina Oliveira, Marta Gómez-Ramiro, Andrea Mallorquí, Victoria Ruiz-Cortés, Yudit Rivas, Silvia Amoretti, Gisela Mezquida, Daniel Ilzarbe, Eduard Vieta, Eduard Parellada, Inmaculada Baeza, Clemente García-Rizo.

Ciudad de celebración: Budapest (Hungria)

Fecha de celebración: 6-9 abril 2024

TABLA DE CONTENIDO

1. Listado de siglas y acrónimos (por orden alfabético)

ATPIII: Adult Treatment Panel III

BNSS: Brief Negative Symptom Scale

CIE 10: Clasificación Internacional de Enfermedades de la Organización Mundial de la Salud

cHDL: colesterol, lipoproteinas de alta densidad

cLDL: colesterol, lipoproteinas de baja densidad

CFCA: Cuestionario de Frecuencia de Consumo de Alimentos

DSM-5: Manual diagnóstico y estadístico de trastornos mentales - Quinta edición

DM2: Diabetes Mellitus tipo II

DIETMED: Dieta saludable como la Dieta Mediterránea

ECV: Enfermedades Cardio Vasculares

ECA: Ensayo Clínico Aleatorizado

EM: Enfermedad Metabólica

FCI-SP: Food Craving Inventory-Spanish versión

FDA: Agencia de Administración de los Alimentos y Medicamentos

HTA: Hipertensión Arterial

IDF: Federación Internacional de Diabetes

IMC: Índice de Masa Corporal

IC: Índice Cintura

ICC: Índice Cintura Cadera

IPAQ: Cuestionario Internacional de Actividad Física

MetS: Score Metabólico para la Resistencia a la Insulina

NICE: Instituto Nacional para la Excelencia en la Salud y la Atención

NCEP: National Cholesterol Education Program

OMS: Organización Mundial de la Salud

PANNS: Escala del Síndrome Positivo y Negativo de la Esquizofrenia

PEP: Primer Episodio Psicótio

PA: Presión arterial

SM: Síndrome Metabólico

TMG: Trastorno Mental Grave

TA: Tensión Arterial

TAD: Tensión Arterial Diastólica

TAS: Tensión Arterial Sistólica

1. Listado de siglas y acrónimos (inglés)

ATPIII: Adult Treatment Panel III

BNSS: Brief Negative Symptom Scale

CIE 10: International Classification of Diseases, 10th Revision

cHDL: high-density lipoprotein) colesterol

cLDL: Low-Density Lipoprotein

DSM-5: Diagnostic and Statistical manual of Mental disorders, fifth edition: DSM-5.

DM2: Type 2 diabetes

FCI-SP: Food Craving Inventory-Spanish versión

FFQ: Food Frequency Questionnaire

FDA: Food and Drug Administration

IMB: Body Mass Index

IDF: International Diabetes Federation

IPAQ: International Physical Activity Questionnaire

MetS: Metabolic síndrome

NICE: National Institute for Health and Care Excellence

NCEP: National Cholesterol Education Program

PANNS: The Positive and Negative Syndrome Scale

WHO: world Health Organization.

2. Resumen

La esquizofrenia es una enfermedad mental que se asocia a un 20% más de mortalidad que la población general, debido a enfermedades como el síndrome metabolico, diabetes Mellitus tipo 2 y/o alteraciones en el peso como la obesidad.

El síndrome metabólico es un marcador de riesgo cardiovascular derivado de presentar un conjunto de factores de riesgo determinados: antropométricos, bioquímicos, y fisiológicos. La presencia de obesidad abdominal, asociado a dislipemia (incremento de triglicéridos o disminución de la lipoproteína de alta densidad asociada al colesterol), hipertensión arterial y hiperglicemia constituyen los marcadores específicos. Dentro de la salud mental y sobre todo de la esquizofrenia la obesidad abdominal es el marcador de riesgo cardiovascular más utilizado para evaluar la salud física de los pacientes. Desde los estudios epidemiológicos de principio de siglo XXI que evidenciaban mortalidad precoz en los pacientes con TMG, debido a una elevada morbilidad médica, se ha intensificado el control de la salud física del paciente diagnosticado de esquizofrenia. Hoy en día sabemos que los pacientes tienen un riesgo aumentado de síndrome metabólico y patología cardiovascular desde etapas iniciales, antes incluso del uso de la toma de psicofármacos, y que aumenta notablemente en los primeros años, llegando a ser hasta 3 veces mayor que en la población general. No solo afecta a la salud física, sino también a la percepción de la imagen corporal del paciente, siendo un factor de riesgo de abandono del tratamiento farmacológico. Se han propuesto diferentes estrategias de manejo del síndrome metabólico; a nivel farmacológico: modificación de dosis, cambio de tratamiento y a nivel conductual: educación dietética, ejercicio físico y cambio de estilo de vida.

El objetivo global de la presente tesis doctoral ha estado el de ampliar el conocimiento en relación aquellos factores que intervienen en el desarrollo de la obesidad y el concepto de síndrome metabólico en la población adulta con esquizofrenia que toman clozapina, así como estrategias para su prevención y manejo.

El primer estudio determina la efectividad de una estrategia de educación para la salud, centrada en alimentación saludable y promoción del ejercicio físico, liderada por una enfermera especialista en salud mental, para prevenir y/o reducir la obesidad y aquellos factores de riesgo cardiovascular: antropométricos, bioquímicos, y fisiológicos en población con TMG que toman clozapina.

Los resultados fueron muy alentadores para seguir en esta línea de investigación, ya que la mayoría de parámetros estudiados mejoraron tras la intervención y algunos de ellos, se mantuvieron hasta pasados los tres meses de esta.

La segunda parte de este trabajo de tesis doctoral se ha centrado en el estudio de la relación existente entre el patrón dietético de nuestra población de estudio y el antipsicotico que tomaban: clozapina, desde que la iniciaban y a lo largo de 18 semanas. En este contexto, los tres estudios que conforman la presente tesis doctoral han querido aportar conocimiento sobre esta relación. Como resultados, se pudo observar que aquellos pacientes que al inicio de tomar clozapina, partían de un bajo peso o normopeso, aumentaban de peso, traducido también, como aumento del IMC. Y este, se correlacionó con que estos pacientes a medida que tomaban clozapina aumentaban los alimentos considerados "antojo" y la frecuencia de consumo de estos y de grasas más saturadas. Por tanto, si que había un cambio en su patrón de alimentación a medida que pasaban las semanas de consumo de clozapina. Los que partían de un sobrepeso/obesidad sí que se observo un aumento de los alimentos antojo, o de los mimos alimentos que consumían previo al inicio de la clozapina pero no se puedo correlacionar de manera significativa con el IMC.

Por último, teniendo en cuenta que la clozapina es un fármaco obesogenico, el último estudio determina hallazgos importantes en relación al frecuente aumento de peso que sufren los pacientes con esquizofrenia que toman clozapina como efecto adverso de esta. Y es que de manera contraintuitiva nuestros hallazgos llaman la atención por la mejoría clínica inesperada asociada con el aumento de peso. Son resultados que se deben tomar con cautela ya que no sabemos totalmente el porque de estos hechos, una explicacion serían las neurohormonas.

Estos trabajos, en su conjunto, quieren arrojar un poco de luz sobre los mecanismos por los que los pacientes que toman clozapina aumentan drásticamente de peso, para poder incidir en ellos, y así, desarrollar estrategias, enfermeras, actuales y de futuro, para su manejo.

3. Introducción

3.1. Esquizofrenia

3.1.1 Esquizofrenia

La esquizofrenia es un trastorno mental altamente incapacitante que afecta alrededor del 1 % de la población y se caracteriza por la aparición de síntomas psicóticos positivos (delirios, alucinaciones, frecuentemente auditivas, desorganización del pensamiento, entre otras…), negativos (apatía, alogia, abulia, aplanamiento afectivo, asociabilidad, etc…) y cognitivos (alteraciones de las funciones ejecutivas como la atención, memoria, etc…) aunque hay mucha variabilidad en la presentación de estos(Jauhar et al., 2022). Los síntomas positivos suelen remitir después del episodio agudo de la enfermedad, aunque algunos pacientes los experimentan en distinta medida a lo largo de toda su vida de manera residual. Por otro lado, los síntomas cognitivos y negativos tienden a cronificarse y están asociados a largo plazo con el grave deterioro a nivel social…etc. La enfermedad suele debutar en la adolescencia o en la adultez temprana, y a menudo se presenta después de lo que llamamos: fase prodrómica, que consiste en un declive de funciones ejecutivas y sociales durante la adolescencia que, a menudo, pasan como imperceptibles para el propio paciente (Jauhar et al., 2022). La enfermedad tiende a manifestarse de manera severa causando lo que llamamos un primer episodio psicótico, es la manifestación abrupta de los síntomas, mayormente positivos, de la enfermedad. La incidencia de esta se encuentra en los 20-24 años para varones, siendo esta algo más elevada (riesgo relativo de 1.4/1) en las mujeres 29-32 años(SA & RM, 2010). Se han descrito diversos factores como posibles causas de la esquizofrenia. Así pues, parece ser que los factores biológicos como la genética y los procesos pre y perinatales (complicaciones durante el embarazo y el parto, malnutrición materna y infecciones) (García-Rizo et al., 2020);

Factores ambientales (impacto de ambientes urbanos, o eventos estresantes en infancia- adolescencia…etc.) o el consumo de tóxicos (Kahn et al., 2015) tienen un impacto en la aparición de la enfermedad. Pero a día de hoy, aun no se conoce con certeza. Así pues, se sigue considerando una enfermedad de origen multifactorial. Su diagnóstico se realiza a través de la historia de salud del individuo y un examen del estado mental de este. Actualmente hay algunas herramientas que se usan en la práctica diaria para ayudar a establecer el diagnóstico médico de esta entidad. La Asociación Estadounidense de psiquiatría creo el Manual *diagnóstico y estadístico de trastornos mentales - Quinta edición: DSM-5* (DSM- V,2013) . Así como la Clasificación Internacional de Enfermedades (CIE) de la Organización Mundial de la Salud, CIE-10 (Bertolote & Sartorius, n.d.). Los mecanismos neurobiológicos que subyacen a los síntomas de la esquizofrenia no están todavía completamente esclarecidos. La teoría más comúnmente aceptada es la hipótesis dopaminérgica, esta se trata de una desregulación en la modulación del sistema dopaminérgico cerebral como resultado de una combinación de múltiples factores de riesgo ambientales y genéticos (Howes & Kapur, 2009).

La mayor parte de personas con esquizofrenia son capaces de llevar una vida adaptada pero funcional con un tratamiento antipsicótico adecuado y de manera continuada. Pero una parte de población con esquizofrenia (25-35%) presentan una forma resistente al tratamiento, por lo cual necesitaran intervenciones más complejas, ya sean farmacológicas y/o psicosociales. Finalmente, otro 10% de esta población mueren por suicido, motivo por el cual es tan necesario la evaluación y seguimiento médico de estas personas.

En relación al curso de la enfermedad, es muy variable. Una parte de la población diagnosticada con esquizofrenia solo sufrirá un episodio psicótico a lo largo de su vida con una remisión completa tras el tratamiento. Otra parte experimentara distintos episodios psicóticos que irán remitiendo y tendrán poca afectación en el deterioro cognitivo y funcionamiento psicosocial. Y finalmente otra parte presentará síntomas psicóticos de forma permanente con un marcado deterioro en todas las esferas de su vida. A lo largo de los años se han podido identificar una serie de factores de buen y mal pronóstico que ayudan a poder generarnos una idea de cómo evolucionar la enfermedad en estos pacientes. Así pues, se considera de mal pronóstico presentar episodios psicóticos con frecuencia, más intensos o de mayor duración ya sea con o sin tratamiento, ya que predisponen a la aparición de síntomas residuales.

A nivel general vemos que hay factores donde no es posible intervenir como son el sexo, la vulnerabilidad epigenética, o el tipo de personalidad previa mientras que otros son claves para definir el pronóstico de la enfermedad. Es imprescindible realizar el diagnóstico temprano para intervenir con rapidez a nivel farmacológico y psicológico.

Se consideran factores de buen pronóstico:

- Sexo femenino.
- Inicio tardío de la enfermedad
- Sin antecedentes familiares relacionados con el espectro de esquizofrenia o historia familiar de trastornos afectivos.
- Buena adaptación previa; Inicio agudo de la enfermedad coincidiendo con factores vitales estresantes.
- Cuadrocon predominio de síntomas positivos versus demás síntomas.
- Buena respuesta al tratamiento farmacológico.
- Cumplimientode la medicación y de los controles.
- Ausencia de alteraciones neuroestructurales en las pruebas de neuroimagen y resultados favorables en les pruebas neuropsicológicas.
- No consumo de sustancias tóxicas.
- Estilo de vida saludable, con rutinas circadianas bien establecidas.
- Cumplimientoestricto de la medicación y de los controles médicos.

3.1.2 Esquizofrenia resistente al tratamiento (refractaria)

Se estima que alrededor de un 20-30% de los pacientes con diagnóstico de esquizofrenia no responden adecuadamente a los psicofármacos convencionales, considerándolos así resistentes al tratamiento. Así, la esquizofrenia resistente al tratamiento se define como una escasa respuesta al tratamiento después de 2 tratamientos con antipsicóticos diferentes, una vez que se asegura la adherencia a la medicación (Kane et al., 2019). La esquizofrenia resistente al tratamiento es de difícil manejo, ya que los pacientes fracasan en múltiples ensayos con antipsicóticos antes de ser considerados dentro de este subgrupo de resistentes al tratamiento. Actualmente, la clozapina es el único fármaco antipsicótico aprobado por la Agencia de Administración de Alimentos y Medicamentos, con sus siglas en inglés (FDA) para la esquizofrenia resistente al tratamiento, pero su prescripción sigue siendo baja por sus efectos adversos: hematológicos y metabólicos y su necesidad de control antropométrico y analítico de manera regular. Como efecto adverso más letal encontramos: la neutropenia, de ahí, la necesidad de controles hematológicos con cierta frecuencia. Además de las mediciones de parámetros metabólicos diversos para mesurar el asociado sobrepeso/obesidad inducida por este fármaco, entre demás alteraciones metabólicas.

3.1.3 Esquizofrenia y clozapina

La clozapina, también más conocida por las marcas comerciales Leponex ® o Nemea ®, fue el primer antipsicótico atípico autorizado. Fue comercializado por primera vez en España en 1975, pero se retiró del mercado en Europa al cabo de poco tiempo a raíz de varios fallecimientos en usuarios de esta medicación por agranulocitosis, el más letal de los efectos secundarios (Mijovic & Maccabe, n.d.). Tras varias investigaciones, fue reintroducido en el mercado por su alta eficacia (Mijovic & Maccabe, n.d.) En Estados Unidos, la FDA lo aprobó para el tratamiento de la esquizofrenia resistente, respecto a otros fármacos, en 1990. En 1993 fue reintroducido en España en respuesta a la necesidad de disponer de una alternativa terapéutica para los casos de esquizofrenia resistente al tratamiento.

En el pasado, su uso era limitado, lo cual se debía en gran parte, al riesgo de agranulocitosis, un trastorno de la sangre que puede llegar a ser letal. Durante todos estos años se ha implementado el uso de analíticas frecuentes para la vigilancia constante de los leucocitos y así tratar satisfactoriamente el riesgo de agranulocitosis. Por tanto, a día de hoy, no hay razón para no prescribirla en los casos que se considere como lo es la esquizofrenia resistente al tratamiento, de hecho, se considera el tratamiento gold estándar en estos casos.

A menudo, cuando un paciente con esquizofrenia no responde al tratamiento, es decir, sus síntomas no están respondiendo al antipsicótico prescrito, se suelen cambiar a otro antipsicótico, en cambio sí se les cambia a clozapina se ha demostrado que tienen una mejoría global (Rubio & Kane, 2020). Tienen menos hospitalizaciones, menos probabilidad de tener que usar otros antipsicóticos adicionales, menor tasa de suicido consumado...etc. Encontramos múltiples estudios en los que han verificado la eficacia de la clozapina en estos casos (Wagner et al., 2021).

La clozapina actualmente está comúnmente comercializada. De manera similar, el Instituto Nacional para la Excelencia en la Salud y la Atención (NICE) del Reino Unido, recomienda la clozapina como el tratamientode elección para los pacientes que no responden a dos antipsicóticos (Kuipers et al., 2014). Así pues, las guías dictan el uso de este fármaco en estos casos, pero debemos tener muy presente las complicaciones cardiometabólicas a medio-largo plazo al elegir este fármaco.

Entre los antipsicóticos de segunda generación, la olanzapina y la clozapina son, de todos, los antipsicóticos que más se asocian con ganancia ponderal, mucho más que otros fármacos de la misma índole (Pillinger et al., 2020). La clozapina se considera generalmente como el fármaco antipsicótico más eficaz, sobre todo, como hemos explicado antes, en casos de esquizofrenia resistente al tratamiento (Leucht et al., 2013), pero entre otros efectos adversos descritos anteriormente, también se ha asociado con un importante riesgo de desarrollar obesidad y complicaciones metabólicas en comparación con otros antipsicóticosatípicos (Pillinger et al., 2020).

Según la Federación Internacional de Diabetes (IDF), la obesidad abdominal es el factor de riesgo individual más importante para el desarrollo de Síndrome metabólico (SM) y Diabetes Mellitus tipo 2 (DM2), por lo que prevenir el aumento de peso, en particular la obesidad abdominal, es esencial para disminuir el riesgo cardio metabólico general y la mortalidad prematura (Zimmet et al., 2007). Se estima que la prevalencia de desarrollo de síndrome metabólico, con sus siglas en inglés, (metS) en pacientes en tratamiento con clozapina oscila entre el 28% y el 45% (Mitchell, Vancampfort, Sweers, et al., 2013).

Lo cual, nos evidencia que gran parte de las personas que toman este fármaco presentaran a lo largo de su vida los distintos componentes que conforman esta entidad o ésta como tal y por tanto, presentaran un riesgo cardio-metabólico elevado (Storch Jakobsen et al., 2018).

El aumento de peso asociado a la gran mayoría de los antipsicóticos es un efecto adverso común. Esto conlleva a varios resultados negativos en los pacientes: riesgo de abandono terapéutico y por tanto de reagudización. El aumento de peso con clozapina se presenta tanto en el momento del tratamiento agudo, como en la fase de estabilización y mantenimiento y puede llegar afectar hasta el 72 % de los pacientes que lo toman. Este impacto en la imagen corporal afecta a su autoestima (Eps_profiles the_atypical_antipsychotics are_not.3, n.d.) y calidad de vida, pudiendo implicar en algunos casos la interrupción del tratamiento.

A día de hoy, la literatura ya describe que cuando los usuarios de clozapina empiezan tratamiento hay un cambio en sus preferencias alimentarias aumentando el consumo de azúcares y grasas poco saludables tipo saturadas o transaturadas como las que encontramos en el tipo de comida"fast food" (Garriga et al., 2019). Esto sumado al tema ya descrito de que las personas con Trastorno mental grave (TMG) tienden a tener una dieta basada en un pobre consumo de fibra, de ciertas vitaminas y minerales y mayor ingesta de carbohidratos refinados de bajo valor nutricional y rico en grasas saturadas, hacen que elempoderamiento en materia de alimentación saludable sea clave en el abordaje terapéutico de esta población para la prevención y/o mejora de la clínica cardiometabolica que acaba siendo la principal causa de muerte de estos pacientes (Dipasquale et al., 2013).

3.1.4 Esquizofrenia y Síndrome Metabólico

La presencia de este síndrome es conocida desde hace décadas bajo diferentes nombres (síndrome X, síndrome de Reaven, síndrome de insulino-resistencia...etc) desarrollado inicialmente en el campo de la endocrinología y cardiología con un doble propósito, clínico y de salud pública.

A nivel clínico para identificar rápidamente a los pacientes y establecer medidas de prevención secundarias y terciarias y a nivel de salud pública para establecer políticas de modificación de los hábitos de vida que puedan incidir en su desarrollo. En materia de salud mental poco se ha avanzado, ya que a pesar del reconocimiento del impacto metabólico de la toma de fármacos antipsicóticos en población con TMG, las políticas de salud poco han cambiado o se han podido modificar a lo largo de estos años (Nielsen et al., 2013).

El síndrome metabólico (MetS) es un conjunto de factores antropométricos, bioquímicos, fisiológicos, que, si se encuentran de manera concomitante y temporal, predicen un aumento de padecer una enfermedad cardiovascular en el futuro. Aunque existen diferentes criterios diagnósticos, los más aplicables en el entorno de la psiquiatría serían los criterios de la IDF (Alberti et al., 2009b) (Tabla1). Esta describe como factor principal y de obligatoriedad la obesidad central (perímetro abdominal, (PC) mayor de 94 cm en varones y 80 en mujeres para europeos, pero con diferentes puntos de corte según el origen étnico y presentar también dos de los cuatro siguientes factores: triglicéridos mayores de 150mg/dL o tratamiento hipolipemiante, HDL menor de 40mg/dL en varones o de 50mg/dL en mujeres o tratamiento hipolipemiante, glucosa en ayunas mayor de 100mg/dL o diagnóstico de diabetes mellitus tipo 2, y tensión arterial sistólica mayor de 130 mmHg o diastólica mayor de 80 mmHg o diagnóstico previo de hipertensión arterial (Alberti et al., 2009a).

Tabla 1.

Indicadores clínicos del síndrome metabólico

Circunferencia de la cintura	
Mujeres	> 88 cm
Hombres	> 102 cm
Triglicéridos séricos	≥150 mg / dL
Colesterol HDL	
Mujeres	<50 mg / dl
Hombres	<40 mg / dL
Presión sanguínea	≥130 / ≥85 mmHg
Glucosa en ayuno	≥100 mg / dL

- (MDe Hert et al., 2011)
- HDL, lipoproteína de alta densidad

Existen otros criterios utilizados, como los del Panel III de Tratamiento de Adultos del Programa Nacional para la Educación sobre el Colesterol de los Estados Unidos (NCEP, ATP III) (Bener et al., 2009); (Wang et al., 2022). Como principal diferencia estos últimos, no exigen la presencia del componente obesidad abdominal. Con todo, los profesionales de la salud mental estamos más acorde con la necesidad del factor obesidad abdominal determinante en los componentes descritos en la IDF ya que estaría más de acuerdo con el subgrupo poblacional que aquí describimos, sujetos con diagnóstico de esquizofrenia que presentan un mayor riesgo de incremento de la masa grasa abdominal por efecto directo de los antipsicóticos.

Es más, en la actualidad, la obesidad abdominal es para diferentes autores el componente esencial del MetS, ya que condiciona el desarrollo de alteraciones glucídicas y a su vez el desarrollo del resto de componentes del MetS (Ritchie & Connell, 2007).

Desde principios de siglo XXI, a partir de los estudios epidemiológicos, se objetiva que los pacientes con esquizofrenia presentan una reducción de la esperanza de vida, entre 10-15 años menor que la población general (Saha et al., 2007). A pesar de la elevada prevalencia de suicidio consumado (Ventriglio et al., 2016), principalmente en los primeros años tras el diagnóstico y el consumo de sustancias tóxicas concomitante (Heiberg et al., 2018); son las patologías cardiovasculares la principal causa de mortalidad en los pacientes (Westman et al., 2018). Las posibles explicaciones de la mayor incidencia de mortalidad en laspersonas con esquizofrenia incluyen la mayor incidencia de obesidad, la mala alimentación y el efecto adverso metabólico de los agentes antipsicóticos (Laursen et al., 2014).

Esta elevada mortalidad está presente incluso desde etapas iniciales de la enfermedad (Nordentoft et al., 2013) sin embargo los estudios en población "*naive"* (sin tratamiento farmacológico previo) sugieren que los componentes del MetS no permitirían establecer diferencias entre pacientes y controles (C Garcia-Rizo et al., 2017). Es en estas etapas iniciales donde se ha objetivado, desde antes de la introducción de los antipsicóticos (McIntyre et al., 2005) la presencia de alteraciones en el metabolismo de la glucosa (Fernandez-Egea et al., 2009) que pronostican una mayor probabilidad de desarrollar DM tipo 2, hecho constatado posteriormente por un metaanálisis (Greenhalgh et al., 2017). Es interesante destacar que este hallazgo no solo afecta a los pacientes afectos de psicosis no afectivas, sino también a las afectivas como esel trastorno bipolar (C. Garcia-Rizo et al., 2014) y trastorno depresivo mayor (Clemente Garcia-Rizo et al., 2013), sugiriendo la presencia de una afectación común en los trastornos mentales graves (Clemente Garcia-Rizo et al., 2016).

La prevalencia de MetS es mayor en las personas con esquizofrenia (Vancampfort et al., 2015a) (Vancampfort et al., 2015b), y en particular en aquellos que tomaban los fármacos tales como la olanzapina y clozapina (Pillinger et al., 2020), como ya hemos comentado anteriormente.

Independientemente del origen de las complicaciones metabólicas en el paciente con diagnóstico de esquizofrenia, lo importante es destacar es que la prevalencia de componentes del Mets en la edad adulta es casi tres veces la de la población general (Marc De Hert et al., 2009), con una prevalencia aproximada del 33% (Vancampfort et al., 2015a), que sin embargo es mucho menor en primeros episodios, aproximadamente del 10% (Mitchell, Vancampfort, De Herdt, et al., 2013) y que consecuentemente incrementa con la edad, el uso de psicofármacos y los hábitos de vida poco saludables (J Bobes et al., 2010).A pesar de lo controvertido del origen de las complicaciones metabólicas en el paciente con diagnóstico de esquizofrenia, lo importante es el hecho de que estos presentan una mayor predisposición, prevalencia y por ende, un mayor riesgo de patología cardiovascular y mortalidad precoz (Kirkpatrick et al., 2014).

Aunque no esté descrito como criterio del MetS, también es necesario destacar el efecto del consumo de sustancias tóxicas, principalmente el consumo de tabaco, por su elevada prevalencia, un hecho descrito hace más de una década (De Leon & Diaz, 2005). Desgraciadamente el consumo de tabaco, no solo "per se" aumenta el riesgo metabólico, sino que también se asocia a menor actividad física y a otros hábitos de vida poco saludables (Julio Bobes et al., 2010). También cabe destacar el consumo de otros tóxicos,asociados a su vez a conductas disruptivas y/o impulsivas que condicionan una mayor incidencia de enfermedades de trasmisión sexual (Chen et al., 2018). Dichas patologías también se asocian a un mayor riesgo cardiovascular y mortalidad precoz.

Otro elemento que se asocia a una mayor mortalidad e influye directamente en el desarrollo del MetS es el estilo de vida de esta población, que, a términos generales, se ha categorizado como poco saludable (Brown et al., 1999). Influenciado tanto por la sintomatología negativa (falta de interés o motivación) o positiva (aislamiento en domicilio por clínica interpretativa fuera de domicilio...etc), precariedadeconómica, entre otras causas. El estilo de vida en la población con esquizofrenia, según la literatura, se caracteriza por escasa o nula actividad física diaria (Bressington et al., 2020) y unos pobres hábitos dietéticos, con una dieta rica en grasas saturadas y pobre en fibra, basada en alimentos procesados y tipo" fast food", muy asociada al desarrollo de MetS (Dipasquale et al., 2013).

El tema de la influencia de los psicofármacos en el MetS es extremadamente controvertido; puesto que aunque hay antipsicóticos que se asocian más a la prevalencia de MetS, principalmente la clozapina y olanzapina (Vancampfort et al., 2015a) y como bien recoge un estudio australiano sobre el tratamiento farmacológico involuntario (Segal et al., 2017), el uso mantenido de tratamiento farmacológico adecuado en pacientes con esquizofrenia, se asocia a una reducción de la mortalidad por patología cardiovascular y/o suicidio.

Por tanto, nos deberíamos centrar en aquellos factores que si podemos modificar y que tienen un impacto directo en el desarrollo del Mets como es el estilo de vida poco saludable. En general, debido a la dimensión del problema de salud física en el paciente con diagnóstico de esquizofrenia y trastorno mental severo, se han desarrollado diferentes guías para el diagnóstico y monitorización de estos problemas (M De Hert et al., 2011). En este aspecto, las mejoras en la formación y por ende, la especialización de la enfermería ha permitido una gran mejora en la atención global del paciente en el día a día de la salud mental. La prevención secundaria y terciaria ha terminado recayendo en el trabajo diario de la enfermería especialista en salud mental (Voogdt-Pruis et al., 2011).

Las diferentes estrategias implementadas para el manejo de la patología cardiovascular y por tanto del MetS en las personas diagnosticadas de esquizofrenia son tanto de tipo ambiental/conductual como farmacológico. En ocasiones están orientadas específicamente a factores de riesgo determinados como el consumo de tabaco o la obesidad y en otras, son aproximaciones generales sobre hábitos de vida saludables.

3.1.5 Intervenciones No farmacológicas para la mejora del estilo de vida en la esquizofrenia

En la actualidad, promover la salud física de los pacientes diagnosticados de esquizofrenia se considera una línea de intervención prioritaria a nivel mundial (Monteleone et al., 2009). Sin embargo, existen dificultades en estos pacientes como poco apego a las intervenciones, falta de motivación…etc., con diferentes estrategias dirigidas a ello, especialmente los programas dirigidos por enfermeras (Chien y Bressington, 2015). La dieta y la promoción del ejercicio físico pueden representar un factor clave para prevenir y mejorar la morbilidad y la mortalidad temprana (Vancampfort et al., 2019). Las comorbilidades médicas no sólo disminuyen la salud cardiovascular, sino que también provocan limitaciones en la vida diaria de los pacientes y un deterioro de su autoestima, todos ellos factores de riesgo para la interrupción del tratamiento (Álvarez-Jiménez et al., 2008).

La literatura actual describe varios estudios en los que solo se evaluaron programas de intervención en el estilo de vida para mejorar la salud física en pacientes diagnosticados con trastorno del espectro de la esquizofrenia (Bonfioli et al., 2012; Vancampfort et al., 2019).

Estudios previos integraron intervenciones sobre alimentación saludable y promoción del ejercicio físico, combinando sesiones individuales y grupales con frecuencia variable basada en elementos conductuales, motivacionales y educativa, realizada por diferentes profesionales de la salud mental (psiquiatras, psicólogos, nutricionistas o enfermeras psiquiátricas). La duración media de estas intervenciones fue de aproximadamente 18 semanas con una mediana de 12 semanas (Bonfioli et al., 2012). Aunque muchos estudios describen este tipo de intervención como eficaz al inicio de la enfermedad, pocos describen cómo controlar el peso y otros parámetros de riesgo cardiovascular una vez que se ha establecido el sobrepeso debido a los antipsicóticos obesógenicos como la clozapina y pocos estudios evalúan los parámetros metabólicos además de la antropometría (Caemmerer et al., 2012). A pesar de la literatura sobre intervenciones farmacológicas y no farmacológicas (Bonfioli et al., 2012; Gierisch et al., 2014; Vancampfort et al., 2019), la heterogeneidad de los estudios limita sus recomendaciones (Faulkner et al., 2010) ysugieren la necesidad de realizar más estudios. Sin embargo, los programas de intervención para la mejora del estilo de vida, dirigidos por enfermeras (Çelik Ince et al., 2018) ,(Mallorquí et al., 2023) han demostrado no solo ser eficaces para mejorar los riesgos cardiovasculares y metabólicos, sino también en la actividad física y la calidad de vida.

Hasta la actualidad, se han investigado diversos tipos de intervenciones para prevenir y/o reducir elaumento de peso producido por los antipsicóticos de segunda generación como es la clozapina. En general las intervenciones conductuales (Papanastasiou, 2012) se agruparían en: programas de promoción a la salud centrados en la práctica del ejercicio físico y consejo dietético; programas de educación nutricional orientados a mejorar la alimentación, manejo del peso y específico para el manejo del sobrepeso y obesidad; Tratamientos cognitivo/conductual orientados a modificar conductas y planteamientos erróneos sobre la salud y programas de psicoeducación orientados a informar al paciente sobre su patología y tratamiento.

Los estados iniciales de la enfermedad son momentos clave para manejar, sobre todo, el incremento ponderal (Pérez-Iglesias et al., 2014). En este sentido hay diferentes estudios que han analizado el manejo del peso del paciente con un primer episodio psicótico desde una orientación psicosocial y de hábitos de vida saludables y que han sido evaluados de forma sistemática con resultados concluyentes de que estas intervenciones son efectivas solo mientras se desarrolla el programa, presentando los pacientes incluidos una menor ganancia ponderal. Hay sin embargo otros factores a considerar en las etapas iniciales, donde el incremento de peso puede dar lugar a un abandono terapéutico. Intervenir en estas etapas puede ayudar a la sensación de bienestar del paciente, evitar la pérdida de autoestima y el consecuente aislamiento social (Álvarez-Jiménez et al., 2008).

Otros estudios que evalúan intervenciones educacionales sobre ejercicio y nutrición en pacientes con diagnóstico de esquizofrenia han sido evaluados de manera sistemática también en diferentes metaanálisis (Mallorquí et al., 2023). Un estudio de 12 semanas realizado por el autor: " Vreeland" en los EE. UU., con 31 usuarios con TMG, incorporó un programa en el que dos veces por semana incluía asesoramiento nutricional, ejercicio y técnicas de asesoramiento motivacional (Bonfioli et al., 2012). Encontraron que el grupo de intervención perdió un promedio de 2,7 kg, mientras que el grupo de control ganó un promedio de 2,9 kg. En este contexto, el estudio presentado en esta tesis, un estudio realizado en una cohorte de pacientes con esquizofrenia en tratamiento con clozapina, demostró que una intervención liderada por una enfermera especialista en salud mental centrada en la promoción y educación nutricional y la práctica del ejercicio físico des del enfoque motivacional, empodero a los paciente en estas materias y mejoro significativamente diversos parámetros metabólicos, además de la reducción en el peso mientras duro la intervención y algunos parámetros se mantuvieron tiempo después (Mallorquí et al., 2023).

La intervenciones cognitivo-conductuales también han aportado ciertas mejorías a la salud física de los pacientes, con terapias grupales, donde se discuten temas como los hábitos dietéticos, el estilo de vida, la actividad física e incluso la percepción subjetiva de bienestar o autoestima con pacientes y a veces también con familiares (Attux et al., 2013).

Pero un elevado número de estudios de revisión y metaanálisis terminan con resultados poco concluyentes (Faulkner et al., 2007). Limitaciones metodológicas propias de las intervenciones en una disciplina como la salud mental tan llena de variabilidad e inconsistencias en ocasiones, como los resultados a evaluar, las intervenciones a realizar e incluso el tipo de paciente y/o tratamiento farmacológico (van Hasselt et al., 2013).

Debido a la elevada heterogeneidad de los estudios incluidos, con tiempos de intervención muy variables, con diferencias entre el tipo de pacientes incluidos (pacientes en unidades de agudos, ambulatorios o en dispositivos de ingreso parcial como son los hospitales de día etc...) es difícil establecer conclusiones definitivas. En líneas generales, los estudios que realizan intervenciones dietéticas son incluidos de manera concomitante con promoción de la actividad física. Sin embargo, pocos estudios muestran resultados específicos, el facilitar fruta y verdura gratis al paciente mejora los hábitos de vida solo mientras esta activo el estudio (McCreadie et al., 2005) o en pacientes en tratamiento con olanzapina el consejo dietético individual implementado por medio de una enfermera y/o un dietista permite reducir el impacto metabólico del tratamiento (Evans et al., 2005). Tenemos que tener en cuenta que las intervenciones, en la mayoría de los estudios, duraron entre 8 y 12 semanas y fueron estudios de metodológica pre-postrecogiendo los resultados al final de la intervención, pocos informaron de periodos de seguimiento largos, estos variaron de 2-3 meses después de finalizar la intervención (Magni et al., 2017).

Es destacable que una visión más analítica de los estudios presentados (Speyer et al., 2019), termina por no recomendar estrategias de intervención individualizada sobre el estilo de vida, pero sí que advierte que posiblemente en grupos determinados (que deberían ser identificados porque actualmente no lo están sí que cumplan con su función de mejoría metabólica. Sin embargo, una visión más clínica, sí que aprecia los beneficios de los programas ambientales, sobre todo teniendo en cuenta que los pacientes presentan unas muy notables dificultades para cambiar sus hábitos de vida poco saludables, así como interiorizar las consecuencias asociadas a factores de riesgo cardiovascular elevados (Hasnain et al., 2011). En resumen,las estrategias de intervención psicosociales al menos desde un punto de vista clínico sí que producen mejoría en la evolución metabólica del paciente con diagnóstico de esquizofrenia, aunque la heterogeneidad clínica nos obliga realmente a establecer diferentes grupos de acción a fin de optimizar los resultados (Gurusamy et al., 2018). Un autor, examino distintas investigaciones donde realizaban intervenciones farmacológicas y no farmacológicas para disminuir el peso en personas con esquizofrenia, de los 18 estudios farmacológicos, con fármacos como: fluoxetina, reboxetina, metformina y topiramato, el uso del tratamiento farmacológico mostro un leve efecto en la prevención de la ganancia de peso. Dado este resultado los autores de las investigaciones concluían que no había suficiente evidencia para apoyar el uso de fármacos para prevenir el aumento de peso (Faulkner et al., 2007) en esta población. Hay que destacar el uso de la metformina, el fármaco concomitante más estudiado asociado con el uso de antipsicóticos para el control metabólico. Un antidiabético oral de la familia de las biguanidas, que ha demostrado un efecto en la mejora del peso, perfil lipídico y sobre todo en los niveles de glucosa y parámetros relacionados como la resistencia a la insulina. Su estudio esta, por tanto, muy ligado al tratamiento con clozapina (Liu et al., 2015) y/o olanzapina (Praharaj et al., 2011). En este contexto existen revisiones concretas que inciden específicamente en tratamientos para disminuir la ganancia ponderal para un determinado fármaco, por ejemplo, la clozapina (Zimbron et al., 2016) muy necesarias en un momento clínico como el actual, donde la falta de nuevas dianas terapéuticas en el mercado está asociada al uso al alza de la clozapina. Aunque existen diversos estudios donde demuestran la eficacia de la metformina para prevenir el aumento de peso y demás complicaciones metabólicas en nuestra población a estudio (Agarwal et al., 2021), la interpretación de los resultados está limitada por el número de estudios, pequeño tamaño muestral y la corta duración de estos estudios (Annamalai & Tek, 2015). La literatura evidencia que puede ser una opción farmacológica eficaz a tener en cuenta para el manejo del aumento de peso inducido por antipsicóticos, después de que los cambios en el estilo de vida hayan fracasado, aunque se precisan de más estudios prospectivos (Annamalai & Tek, 2015).

Aunque es un tema que despierta interés por sus posibles beneficios en nuestra población a estudio, en nuestro país no es legal la prescripción de metformina para personas que no estén diagnosticadas de DM II, por sus efectos secundarios a largo plazo (Annamalai & Tek, 2015).

Por tanto, actualmente no es una vía a tener en cuenta, dando un mayor peso a la necesidad de intervenciones enfermeras efectivas como la descrita en esta tesis doctoral de modificación del estilo de vida para prevenir y/o mejorar los parámetros de riesgo cardio metabólicos relacionadas con la propia obesidad y los fármacos antipsicóticos.

La literatura evidencia que puede ser una opción farmacológica eficaz a tener en cuenta para el manejo del aumento de peso inducido por antipsicóticos, después de que los cambios en el estilo de vida y la dieta hayan fracasado.

4. Objetivos

4.1 Generales:

4.1.1 Medir los parámetros: peso, IMC, IC, ICC a nivel antropométrico. A nivel metabólico: TA, Colesterol total, Colesterol HDL y LDL, triglicéridos y glucosa, antes y después de una intervención de educación para la salud basada en alimentación saludable y promoción del ejercicio físico, de 8 semanas de duración, y 3 meses después de esta, para personas con esquizofrenia en tratamiento con clozapina.

4.1.2 Evaluar los cambios a nivel de preferencias alimentarias, antropometricos, y psicopatológicos en personas con esquizofrenia antes de inciar clozapina, a las 8 semanas y a las 18 semanas de tratamiento.

4.2 Objetivos específicos:

Publicacion nº 1: *Nurse-led lifestyle intervention in a cohort of schizophreniapatients treated of clozapine.*

En este contexto dentro del objectivo general 4.1.1 propusimos los siguientes objetivos especificos relacionados con la publicación nº1:

- Evaluar los cambios a nivel antropométrico, metabólico y de estilo de vida antes y después de una intervención de educación para la salud basada en alimentación saludable y promoción del ejercicio físico en pacientes con esquizofrenia refractaria en tratamiento con clozapina por psicosis resistente.

- Evaluar la adherencia a la dieta mediterránea a través de la escala DIEMED, del ejercicio físico a través del Cuestionario IPAQ antes y después de una intervención de educación para la salud basadaen alimentación saludable y promoción del ejercicio físico, de 8 semanas de duración, y 3 meses después de esta, para personas con esquizofrenia en tratamiento con clozapina.

Publicación nº 2*: Food craving and consumption evolution in patients starting treatment with clozapine.*

En este contexto dentro del objectivo general 4.1.2 propusimos los siguientes objetivos especificos relacionados con la publicación nº2:

- Describir las preferencias alimentarias específicas (alimentos antojo) y la frecuencia de consumo de los distintos grupos de alimentos en pacientes con TMG que inician clozapina, a las 8, y 18 semanas desde el inicio del tratamiento.
- Correlacionar estas preferencias alimentarias y el consumo específico de tipos de alimentos con el peso (kg) y el índice de masa corporal (IMC).

Publicación nº 3: *Antipsychotic-Associated Weight Gain and Clinical ImprovementUnder Clozapine Treatment.*

En este contexto dentro del objetivo general 4.1.2 propusimos los siguientes objetivos específicos relacionados con la publicación nº2:

- Evaluar la asociación entre la mejoría clínica, medida por la escala de la (PANSS), debida al tratamiento con clozapina y el cambio antropométrico al inicio del tratamiento con clozapina, a las 8 y 18 semanas de tratamiento.

- Evaluar si se observan diferencias significativas por sexo en la mejoría clínica debida al tratamiento con clozapina y el cambio antropométrico al inicio del tratamiento con clozapina, a las 8 y 18 semanas de tratamiento.

5. Publicaciones Cientificas

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Nurse-led lifestyle intervention in a cohort of schizophrenia patients treated with clozapine

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ABSTRACT

Patients diagnosed with schizophrenia are characterized by early mortality compared to the general population. The main cause of this premature death reflects medical complications linked to metabolic syndrome (MetS). The use of antipsychotics such as clozapine is associated with weight gain and metabolic disturbances in certain predisposed individuals. Non-pharmacological interventions for weight control have become a key element for secondary prevention in the health of patients diagnosed with schizophrenia. Here, we aim to evaluate the physical health effects of a nurse-led non-pharmacological intervention program in patients with a diagnosis of schizophrenia treated with clozapine.

Thirty-one outpatients from the outpatient clinical facility of Hospital Clinic in Barcelona, Spain diagnosed with schizophrenia and other psychotic disorders receiving clozapine treatment were enrolled in a prospective interventional study, comprising an 8-week group program of therapeutic education in a healthy lifestyle. MetS factors, physical activity, diet, and lifestyle were evaluated at baseline, post-intervention (8 weeks), and 3 months after the program. Weight, body mass index, high-density lipoprotein cholesterol, and diet patterns displayed significant differences post-intervention and after 3 months, while only waist, hip perimeter, and lifestyle improved post-intervention.

Our results suggest the effectiveness of the lifestyle intervention in patients under clozapine treatment despite its long-time differential effect. Strategies to prevent weight gain and metabolic decline will help prevent pre- mature cardiometabolic disease in this vulnerable population.

Introduction

Serious mental illness remains one of the leading causes of global disease burden (GBD 2019, 2022). Among these is schizophrenia that stands out as a disease with a high impact on physical health associated with a high risk of morbidity and early mortality (Kirkpatrick et al., 2014), leading to a high burden of disease. The etiology of schizophrenia is understood to involve a complex interaction of genetic, biological, and

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social factors. It has a prevalence of approximately 1 % in the general population while the life expectancy of those who suffer from it is reduced by approximately 10 to 20 years, compared to the general population (Hjorthøj et al., 2017). Although a proportion of this excess mortality is caused by suicide and poor adherence to health services, a large part is related to cardiovascular diseases (CVD) and metabolic syndrome (MetS) related diseases (Ringen et al., 2014). In a national register study, (Westman et al., 2018) the excess of death by CVD was reported to be almost three times higher than by suicide, although different suicide rates have been described depending on psychotic subtypes, clinical setting, and geographical region (Á lvarez et al., 2022). MetS is defined as a cluster of different risk factors: biochemical and physiological, which predicts the development of CVD and type 2 Diabetes Mellitus over time. Different diagnostic criteria are utilized, but the most applicable in the context of psychiatry are the criteria developed by the International Diabetes Federation [IDF] (Alberti et al., 2006) that apply an abdominal perimeter requirement. Several pathophysiological aspects are related to the morbidity and mortality of schizophrenia, such as the genetic predisposition of these individuals to suffer from cardiometabolic disorders (Segura et al., 2022), prenatal events (Garcia-Rizo et al., 2020, 2022; Garcia-Rizo & Bitanihirwe, 2020; Garriga, Fernandez-Egea, et al., 2019a), unhealthy lifestyles (Heald et al., 2017) and pharmacological treatment (Pillinger et al., 2020). Thus the age-standardized MetS prevalence in the general population has been described to be higher in men (38.37 %) than in women (29.62 %) (Marcuello et al., 2013) while in patients diagnosed with schizophrenia stands similar but for subjects 10 to 15 years older suggesting an accelerated aging process (Kirkpatrick et al., 2008).

Regarding lifestyle, it has been well described that lack of physical activity, poor dietary habits, and rates of tobacco consumption are particularly high in this population (Firth et al., 2020). A low socioeconomic status, sedentary lifestyle and preference for an eating pattern characterized by saturated fats, sugars refined, and low fiber (Jakobsen et al., 2018) are also suggested to play a substantial role in the pathogenesis of the disease. On the other hand, pharmacological treatments, especially antipsychotics, including clozapine, are associated with significant weight gain, which does not help an unhealthy lifestyle (Gurrera et al., 2022). Clozapine is the antipsychotic prescribed to psychosis- resistant patients. In a recent systematic review and network meta- analysis of 32 antipsychotics, clozapine displayed the best results for overall change in symptoms and negative symptomatology (Schneider- Thoma et al., 2022). Indeed, it is more effective than other drugs in those with suicidal ideation (Masdrakis & Baldwin, 2023) while presenting a low propensity to cause extrapyramidal side effects (Schneider-Thoma et al., 2022). Despite these advantages, clozapine is under-prescribed due to the fear of certain side effects, some of which are potentially le- thal, such as agranulocytosis (Li et al., 2018).

Therefore, clozapine administration should be closely monitored by the medical team, since its use also leads to a higher prevalence of MetS (Whitney et al., 2015) while being associated with a significant increase in hunger and/or lack of satiety and the propensity to choose certain nutrients such as "fast food" style fats (Garriga, Mallorquí, et al., 2019b). Clozapine side-effects require rigorous control and monitoring of anthropometric and analytical parameters, which makes treatment adherence difficult in patients with severe mental illness.

Patients diagnosed with schizophrenia are at increased risk for undetected, late, and inadequately treated medical conditions (Thorni- croft, 2011), which also contribute to early mortality due to modifiable factors detected at the initial stages of the mental illness (Smith et al., 2020). Often these are not detected in time and lead to MetS and end up having a negative impact on their physical health and quality of life.

At present, promoting the physical health of patients diagnosed with schizophrenia is considered a priority line of intervention worldwide (Maj, 2009). However difficulties exist (low attachment to in- terventions, lack of motivation) with different strategies aimed at it, especially nurse-led programs (Chien & Bressington, 2015). The diet and promotion of physical exercise can represent a key factor to prevent and improve morbidity and early mortality (Vancampfort et al., 2019). Medical comorbidities not only decrease cardiovascular health but also lead to limitations in the daily living of patients and a deterioration of their self-esteem, all risk factors for treatment discontinuation (Á lvarez-Jiménez et al., 2008). Current literature describes various studies in which only lifestyle intervention programs were evaluated to improve physical health in patients diagnosed with schizophrenia spectrum dis- order (Bonfioli et al., 2012; Vancampfort et al., 2019). Previous studies integrated interventions on healthy eating and the promotion of physical exercise, combining individual and group sessions with variable fre- quency based on behavioral, motivational, and educational elements while being carried out by different mental health professionals (psy- chiatrists, psychologists, nutritionists, or psychiatric nurses) (Refer- ences). The mean duration of these interventions was approximately 18 weeks with a median of 12 weeks (Bonfioli et al., 2012). Although many studies describe this type of intervention as effective at the onset of the disease, fewer describe how to manage weight and other cardiovascular risk parameters once overweight has been established due to obesogenic antipsychotics such as clozapine with few studies evaluating metabolic parameters besides anthropometry (Caemmerer et al., 2012). Despite the literature on pharmacological and non-pharmacological interventions (Bonfioli et al., 2012; Gierisch et al., 2014; Vancampfort et al., 2019), the heterogeneity of the studies limits its recommendations (Faulkner et al., 2010) and suggest the need of further studies. Nevertheless, nurse-led intervention programs (Çelik İnce & Partlak Günüşen, 2021; Chien et al., 2015; Fernández Guijarro et al., 2019; Rönngren et al., 2018) have proved not only effective in improving in cardiovascular and metabolic risks but also in physical activity and quality of life.

Against this background, the present study aims to analyze the physical health effectiveness of an intervention program in patients diagnosed with schizophrenia treated with clozapine.

Material and methods

Study design and subject selection

A prospective interventional study was conducted in a cohort of patients diagnosed with schizophrenia and other psychotic disorders (27 diagnosed with schizophrenia and 4 diagnosed with schizoaffective disorder) treated with clozapine. A mental health advanced practice nurse conducted the study procedures.

The study comprised an 8-week group program of therapeutic education in healthy lifestyle along with three visits where analytical, anthropometrical, and clinical parameters were collected. The timeline of the three visits was: (1) at baseline (the previous week that the therapeutic program started), (2) at week 8 (the week after the thera- peutic program was finished), and (3) at 3 months after the end of the therapeutic program.

The study included 31 psychiatric outpatients diagnosed with schizophrenia and other psychotic disorders that were under pharmacological treatment with clozapine in the outpatient facility of the Hospital of Barcelona (Barcelona, Spain). Patients were treated with clozapine for at least one year but could also been receiving treatment with other pharmacological agents in relation to their psychopathology.

Inclusion criteria were: (1) patients diagnosed with schizophrenia and other psychotic-related disorders according to the DSM-V criteria; (2) aged from 18 to 65 years old. The exclusion criteria were: (1) a history of traumatic brain injury and (2) mental retardation. Each sub- ject was informed of the purpose, procedures, and potential risks of participation in the study before signing an informed consent form. The protocol was approved by the local Ethical Committee and conducted in conformity with the Declaration of Helsinki.

Intervention

An 8-week group program of therapeutic education in healthy lifestyle

A dietary and lifestyle program was developed based on nutritional education and physical exercise, adapted from a similar intervention in patients with Type II Diabetes Mellitus (Colungo et al., 2018). Content of the intervention was structured in PowerPoint format that was spec if- ically developed for this study. Eight weekly structured sessions were held lasting 1 h and a half comprised of: 2 sessions related to unhealthy lifestyle and its metabolic consequences in schizophrenia; 3 sessions related to educational diet education; 1 session about promoting phys- ical exercise; and 2 sessions focused on practical aspects of diet plani- fication and problem-solving). The intervention was conducted in a group setting, with 9 to 12 subjects in each group.

Demographic, clinical, anthropometric, and metabolic measures

The baseline visit involved gathering of demographic and clinical data that was collected via a questionnaire designed for this study. All patients fulfilled DSM-V (American Psychiatric Association, 2013) diagnostic criteria for schizophrenia. Data on antipsychotic treatment, tobacco use, and previous presence of cardiovascular risk factors (up to 13 items linked to modifiable cardiovascular risk factors were assessed), were explored on the study visits by trained staff. Blood sampling was obtained by venipuncture after 8 to 10 h of food fasting. Anthropometric and hemodynamic parameters collected at each study visit included; weight as measured in kilograms, with participants in their underwear, barefoot, standing in the center of the scale with their arms by their side, and the weight distributed on both feet; height was measured in centi- meters, with participants standing barefoot and with their feet together; waist circumference was measured in centimeters at the end of a gentle expiration; hip circumference was measured in centimeters, it was considered the maximum value achieved by surrounding the hip hori- zontally with the tape; body mass index (BMI) was calculated by dividing the weight in centimeters by the square of the height in meters

(BMI = weight [kg]/height2 [m2]), BMI status was determined ac- cording to the World Health Organization definition: BMI <18.5 kg/m2, underweight; 18.5 to 25 kg/m2, normal weight; 25 to 30 kg/m2,

overweight; and BMI 30 kg/m2 or greater, obese (Onis, 2006); waist/hip ratio was calculated by dividing the waist circumference in centimeters by the hip circumference in centimeters. According to the WHO, values

<0.8 in women and 1 in men are considered (World Health Organi- zation. Retrieved March 21, 2008); Heart rate was determined using an

Omron M3 Intellisense digital arm blood pressure monitor. Considering normal values of 60–120 beats/min (Zhang & Zhang, 2009); Blood pressure was determined using an Omron M3 Intellisense digital arm blood pressure monitor. Two measurements were made, spaced 10 min apart, with the patient in a sitting position and after the remaining 5 min at rest. The arithmetic mean of the two measurements was made.

Health questionnaires

EQ-5D Health Questionnaire Spanish version

As part of the assessment of health-related quality of life, the Spanish version of EQ-5D was used (Badia et al., 1999). The EQ–5D is a brief health status measure composed of five questions with Likert response options (descriptive system) and a visual analog scale. The descriptive system covers five dimensions of health (mobility, self-care, usual ac- tivities, pain/discomfort, and anxiety/depression) with three levels of severity in each dimension (no problems, some problems, and extreme problems). The visual part assesses the overall health status of the pa- tient on a score between 0 and 100 (where the highest imaginable state of health should be marked with a 100 and the worst with a 0) in relation to how they feel at the time (Janssen et al., 2008).

The International Physical Activity Questionnaire-Short Form (IPAQ-SF)

The International Physical Activity Questionnaire (IPAQ) was designed to measure the level of physical activity that you do in your daily life over the last 7 days (Hagstr¨omer et al., 2006). It is a ques- tionnaire for the evolution of physical activity in subjects between 18 and 69 years of age. In the present study, its short form was used (IPAQ- SF) (Roman-Vi˜nas et al., 2010), which has been recommended when the objective of the study is population monitoring. The IPAQ-SF consists of

6 items about various dimensions of physical activity that include walking, moderate-intensity (e.g., carrying light loads, cycling at a regular pace), and vigorous-intensity (e.g., heavy lifting, digging, aer- obics) activity in terms of both the duration (in minutes/day) and fre- quency (days/week) and one item about the duration (in minutes/day) of sedentary behaviour. The unit of measurement for weekly physical activity is recorded in the Metabolic Equivalent of Task-minutes/week (MET-m/w). The reference METs are 1. For walking: 3.3 METs; 2. For moderate physical activity: 4 METs; and 3. For vigorous physical ac- tivity: 8 METs. The final value of the questionnaire corresponds to the product of the intensity (in METs), by the frequency, by the duration of the activity, and finally, the subjects are classified into 3 categories: 1 Low level or inactive; 2. Moderate level; and 3. High level of activity.

Dietary questionnaires

Questionnaire of Mediterranean diet adherence

The Mediterranean diet test is based on the PREDIMED test (Zazpe et al., 2008). This is a brief instrument for assessing nutritional habits made up of a set of 14 simple questions related to the consumption of certain foods and their frequency of consumption. The evaluation of these questions aims to offer information about the adherence of the Spanish population to the recommended Mediterranean diet. The sum of the values of each response (0–1) gives rise to an index that is classified

into two categories: <7 points of the total responses indicates a poor adherence to the Mediterranean diet and above 10 indicates a good adherence to the Mediterranean diet (Estruch et al., 2006).

Statistical analysis

Descriptive statistics were used to present baseline demographic, clinical, and anthropometric characteristics. Continuous variables were expressed as the median and their 95 % confidence intervals (95 % CI). Qualitative variables were presented as absolute frequency and percentage.

To longitudinally assess changes from baseline, statistical analyses were performed by using generalized estimating equations (GEE) models, with an estimation of within-subject correlation from an autoregressive approach (AR(1)). The use of GEE was performed to handle missing data and time-dependent covariates properly while using median values due to the small sample size. Results are expressed as mean and 95 % confidence intervals. When analyzing longitudinal studies, for outcomes that are repeated during follow-up, measures are correlated across subjects, and some may be missing. In these cases, Liang and Zeger proposed the GEE methodology as a valid approach (Liang & Zeger, 1986). This methodology has some assumptions about the generation of missing data. Such missing data could be estimated from the intra-subject correlation and the covariates in the model. In our case, it can be assumed that these missing data are representative ofclinical practice for these patients, not caused by participation in research. It is therefore plausible to consider that the losses to follow-up of the 31 patients are due to the characteristics of their baseline char- acteristics and their clinical evolution. Since the analysis with GEE models solves the problem of missing data longitudinally, a different sample size per follow-up visit should not be considered, the result being the model estimate and not the visit-by-visit result by repeated analysis of independent statistical tests, such as Student's *t*-test or Chi-square.

P value ≤0.05 was considered statistically significant, and all

calculations were performed with SPSS version 25 (IBM) software. Due to the observational nature of characteristics in this study, no formal sample size calculation was performed and no methods for multiplicity were performed.

Results

A total of 31 participants were recruited and completed the 8-week program. Sociodemographic and clinical characteristics, as well as anthropometric and metabolic measurements on baseline and follow-up visits, are presented in Tables 1 and 2.

Anthropometric outcomes

From baseline, weight and BMI decreased significantly at the end of the intervention and three months later (for weight: $p < 0.001$ and $p = 0.010$, respectively; for BMI: $p = 0.003$ and $p = 0.030$, respectively). Other anthropometric measures where positive changes were observed between baseline and the end of the intervention included hip circumference and waistline (p=0.030 for waist and p =0.015) but these changes did not hold three months post-intervention. However, when calculating the waist/hip ratio, only changes from baseline to three months after the intervention were significant ($p = 0.017$).

Metabolic parameters

Fasting glucose levels as well as levels of LDL-cholesterol and triglycerides did not improve following the intervention. However, some measurements from the cholesterol profile improved significantly post intervention. Notably, levels of HDL-cholesterol significantly improved at the end of the intervention ($p = 0.036$) and maintained a level of significant improvement 3 months after the intervention ($p < 0.05$). Total cholesterol level only improved significantly at 8 weeks ($p = 0.046$).

Health and dietary questionnaires

Although subjective perception of overall health did not change during the study period (according to the visual scale of the EQ-5D), patients did, however, improve in their adherence to the Mediterranean diet at both follow-up study visits (p 0.011 and p 0.017, respectively). That aside, patients presented clinical changes in physical activity during the program (f.i. the number of patients who scored as inactive/low according to the IPAQ scale decreased from 23 to 18 after the intervention and back to 21 after 3 months, while patients who scored moderate/high increased from 7 to 11 and back to 8 respectively).

Discussion

Our results confirm findings from previous studies where non-pharmacological interventions can significantly reduce cardiometabolic risk and improve lifestyle (Bonfioli et al., 2012; Bruins et al., 2014; Caemmerer et al., 2012; Fern´andez-San-Martín et al., 2014; Gierisch et al., 2014; Hjorth et al., 2014; Speyer et al., 2019) in a cohort

Table 1
Clinical and socioeconomic variables of the sample.

Age (years old) (95%CI)	45.0 (21.4–58.4)
Sex (female)	45 % (*N* = 14)
Marital status (single)	87 % (*N* = 27)
Educational level	Primary school 45 % (N = 14) High school 10 % (*N* = 3) University 19 % (*N* = 6)
Employment status	Disability 48 %(*N* = 15) Currently working 29 % (*N* = 9) Unemployed 16 % (*N* = 5)
Smoking	Yes 35 % (*N* = 11) No 55 % (*N* = 17)

Table 2
Descriptive anthropometric clinical and metabolic variables and significant changes from baseline (Mean and 95 % Confidence Interval).

Mean (95 % CI)	Baseline	At week 8	3 months after the intervention
Weight (Kilograms)	95.39 (87.69; 103.09)	92.09 (84.60; 99.59)	93.92 (84.17; 103.66)
(Pounds)	*210.3 (193.32; 227.27)*	*203.02 (186.51; 219.56)*	*207.06 (185.56; 228.53)*
	N = 30	**(p < 0.001)**	**(p ¼ 0.010)**
BMI (Kg/m²)	32.64 (30.36; 34.92)	*N* = 29 31.73 (29.46; 33.99) **(p ¼ 0.003)**	*N* = 20 32.43 (29.33; 35.54) **(p ¼ 0.030)**
	N = 30	N = 29	N = 20
Waist (Centimeters)	112.33 (106.93; 117.74)	110.68 (105.45; 115.91)	112.08 (105.47; 118.68)
(Inches)	*44.22 (42.09; 46.35)*	*43.57 (41.51; 45.63)*	*44.12 (41.52; 46.72)*
	N = 30	**(p ¼ 0.003)**	(*p* = 0.106)
		N = 28	N = 20
HIP (Centimeters)	111.77 (107.28; 116.26)	110.50 (106.00; 115.00)	113.42 (108.11;118.73)
(Inches)	*44.00 (42.23; 45.77)*	*43.50 (41.73; 45.27)*	*45.27 (42.56; 46.74)*
	N = 30	**(p ¼ 0.015)**	(*p* = 0.919)
		N = 28	*N* = 19
WHR	1.00 (0.98; 1.03) 0.39 (0.38; 0.40)	1.00 (0.98; 1.03) 0.39 (0.38; 0.40)	0.99 (0.95;1.02) 0.38 (0.37; 0.40)
	N = 30	(*p* = 0.372)	**(p ¼ 0.017)**
		N = 28	N = 19
SBP (mm Hg)	121.87 (118.52; 125.22)	122.00 (118.26; 125.74)	122.10 (115.32; 128.88)
	N = 30	(*p* = 0.953)	(*p* = 0.345)
		N = 29	N = 20
DBP (mm Hg)	80.30 (77.43; 83.17)	78.24 (75.76; 80.72)	76.05 (71.88; 80.22)
		(*p* = 0.060)	(*p* = 0.070)
	N = 30	N = 29	N = 20
HR (bpm)	86.83 (82.38; 91.28)	83.14 (77.95; 88.33)	85.71 (81.35; 90.08)
	N = 30	(p = 0.10)	(*p* = 0.462)
		N = 28	*N* = 21
Glucose (mg/dL)	117.29 (92.96; 141.61)	108.72 (90.08;127.36)	117.36 (73.95; 160.76)
	N = 28	(*p* = 0.749)	(*p* = 0.492)
		N = 24	N = 14
Total-cholesterol (mg/dL)	198.21 (185.06; 211;37)	192.80 (175.61;209.99)	195.00 (171.08; 218.92)
	N = 28	**(p ¼ 0.046)**	(*p* = 0.671)
		N = 24	N = 11
LDL (mg/dL)	122.33 (109.17; 135.50)	121.26 (107.69; 134.83)	114.75 (89.79;139.71)
	N = 24	(*p* = 0.168)	(*p* = 0.101)
		N = 22	*N* = 8
HDL (mg/dL)	42.14 (37.54;46.75)	45.58 (41.04;50.13)	43.80 (36.74;50.86)
	N = 28	**(p ¼ 0.036)**	**(*p* ¼ 0.050)**
		N = 24	*N* = 10
Triglycerides (mg/dL)	158.79 (120.60; 196.97)	150.05 (108.91; 191.20)	210.00 (49.65; 370.35)
	N = 28	(p = 0.168)	(*p* = 0.933)
		N = 24	N = 11

BMI: Body Mass Index. WHR: Waist Hip Ratio. SBP: Systolic Blood Pressure. mm Hg: millimeter of mercury.
DBP: Diastolic Blood Pressure. HR: Heart Rate. bpm: beats per minute. HDL: High-Density Lipoprotein. LDL: Low-Density Lipoprotein.

of treatment-resistant patients	diagnosed with schizophrenia under clozapine treatment. Ex-smoker 10 % (N = 3)	Nevertheless, our results show not only a short-term improvement but also a medium-term improvement (3 months of post-intervention).

Thus, regarding specific anthropometric variables such as weight or BMI, our results showed a reduction which was maintained during the three months after the intervention, as shown in the majority of the literature reviewed (´Alvarez-Jime´nez et al., 2008; Fern´andez-San-Martín et al., 2014). However other studies did confirm previous results (Lovell et al., 2014; Masa-Font et al., 2015).

Nevertheless, other anthropometric variables such as waist and hip measurements showed an improvement after the intervention but were not maintained after 3 months of the intervention. Similar findings were described by the Australian Keep Body in Mind program involving patients diagnosed with a first episode of psychosis, which improved the number of participants who decreased their initial weight by over 7 % but did not remain beyond the three months post-intervention (Watkins et al., 2019). Interestingly, in our sample, waist-to-hip ratio showed a significant reduction three months after the intervention. The waist-to- hip ratio is an accurate anthropometric indicator to predict arterial hypertension and cardiovascular risk and today is considered one of the best predictors of cardiovascular risk beyond BMI (Czernichow et al., 2011). Therefore, its improvement three months after finishing the lifestyle sessions demonstrates the effectiveness of the intervention in reducing one of the major predictors of cardiovascular risk. As such, it can be considered a good strategy to modify MetS parameters in this vulnerable and complex population for which few non-pharmacological interventions have been beneficial.

Biochemical parameters such as HDL-cholesterol were significantly reduced both in the post-intervention measurement and at 12 weeks while total cholesterol only just after the intervention suggesting that participants during the sessions managed to modify their eating habits, leaving aside the tendency for foods rich in saturated fat and carbohydrates of low nutritional quality (Aucoin et al., 2020), in addition to fast food due to greater consumption of fruits, vegetables and high-quality proteins (McCreadie et al., 2005). Other cardiovascular parameters such as blood pressure or heart ratio did not show any statistical reduction despite a clinical improvement. Nevertheless, and despite the lack of statistical improvement, from a clinical perspective, an improvement was observed with its positive consequences in the sub- jective perception of the patients involved.

Another important finding is the evolution of the dietary patterns, as our results show a significant and maintained improvement not only after intervention but after 3 months. Similar findings have been described in another study where weight improvement was maintained even 3 months after finishing the intervention period based on nutrition education provided by a dietitian (Evans et al., 2005).

Antipsychotic side effects contribute significantly to the high rates of weight gain and obesity, and to alterations in the metabolic profile of people with SMI (Pillinger et al., 2020). However, the feasibility of an intensive 12-week program, achieving knowledge and modifying their eating pattern, seems to slow down the evolution of more severe cardiometabolic diseases (Speyer et al., 2019). We observed that most of the subjects, in addition to following an unhealthy diet, presented with moderate physical inactivity, along with high rates of cigarette smoking (Scott & Happell, 2011), each of which represent phenomena that should be detected early and monitored by policy makers due to its impact on physical health. Thus, a systematic screening of metabolic profiles in SMI patients under antipsychotic treatment that are highly associated with weight gain, such as clozapine, is required. An effective lifestyle intervention with 'sustained results' is necessary for a global approach toward reducing the mortality gap in schizophrenia.

On the other hand, our study suggests that the metabolic secondary-side effects of clozapine (Pillinger et al., 2020) can be managed in the short term. Therefore, it should not impede its therapeutic use (Verdoux et al., 2018). In this regard, delegating the metabolic management of these weight-promoting antipsychotics to psychiatric nurses with advanced roles (Clark et al., 2014; Gage et al., 2015; Sanjeevi & Coco- man, 2020) would represent a benefit for the physical health of SMI patients without compromising the safety of taking this treatment, and they also represent a low cost for the health system, improving the quality of patients' lives.

This study has a several imitations, among which the size of the sample and the lack of controls related to the characteristics of age, sex, and socio-demographics stand out. This was due to the nature of this study, which aimed to assess the efficacy of a lifestyle intervention in the real world, and which was offered to all subjects who met the inclusion criteria for a mental health intervention so that randomization and subsequent comparison could not be carried out.

To date, the literature reviewed does not reveal any experimental studies in line with the present work, which makes the results of this study led by a nurse open a door to new research (Chien & Bressington, 2015). Having an integrated lifestyle program within the mental health system applied to people diagnosed with SMI would improve and promote greater attendance at the mental health center, which allows additional opportunities to contact mental health doctors for a population with low access to health services. Nevertheless, and as usually happens in these cases, larger and less methodological heterogeneity studies are needed to confirm these findings (Faulkner et al., 2007).

Mental health nurses are an essential part of outpatient facilities, and due to their close contact with SMI patients can monitor cardiovascular risk and lifestyle. Non-pharmacological interventions such as thera- peutic education on health promotion led by a psychiatric nurse are easy to implement and with reduced economic cost while effective over the long-time course and improve the physical health of patients diagnosed with schizophrenia. Taken together, the findings from this study suggest that nurse-led lifestyle intervention programs can improve the quality of life of SMI patients and highlight the need for healthier lifestyle habits to reduce the increased morbidity and early mortality described in patients diagnosed with schizophrenia.

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Declaration of competing interest

Authors do not declare any conflict of interest on this study.

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Food craving and consumption evolution in patients starting treatment with clozapine

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Abstract

Background Antipsychotic-induced weight gain has been especially related to clozapine and olanzapine. Underlying mechanisms in relation to food preferences with an increased food craving and consumption of specific nutrients have not been extensively studied in patients with serious mental illness (SMI). We aim to describe specific food preferences (craving) and subsequent food consumption in SMI patients starting clozapine, as well as their possible relation to weight and body mass index (BMI).

Methods An observational prospective follow-up study (18 weeks) was conducted in a cohort of 34 SMI patients who started clozapine due to resistant-psychotic symptoms. Anthropometric measures, Food Craving Inventory (FCI), and a food consumption frequency questionnaire were evaluated at baseline, weeks 8 and 18 of treatment. Statistical analysis included generalized estimating equations models with adjustment for potential confounding factors.

Results No longitudinal changes over time were found across the different food craving scores after 18 weeks of treatment. However, adjusted models according to BMI status showed that the normal weight (NW) group presented an increased score for the ʙcomplex carbohydrates/proteins^ food cravings (− 0.67; 95% CI [− 1.15, − 0.19]; $P = 0.010$), while baseline scores for ʙfast-food fats^ cravings were significantly higher in the overweight/obese (OWO) group in comparison with NW patients (NW, 2.05; 95% CI [1.60, 2.49]; OWO, 2.81, 95% CI [2.37, 3.25]; $P = 0.016$). When considering if food craving could predict weight gain, only increments in ʙfast-food fats^ cravings were associated ($\beta = -5.35 \pm 1.67$; 95% CI [− 8.64, − 2.06]; $P = 0.001$).

Conclusions No longitudinal differences were found for any of the food craving scores evaluated; however, in the NW group, food craving for ʙcomplex carbohydrates/proteins^ changed. Thus, changes in fast-food fats^ cravings predicted weight increase in this sample. Interventions targeting food preferences may help to mitigate weight gain in patients starting treatment with clozapine.

Keywords Antipsychotic-inducedweightgain · Clozapin · Food Craving Inventory(FCI) · Seriousmentalillness

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Introduction

The prevalence of antipsychotic prescription has increased over the past decades (Ilyas and Moncrieff 2012; Olfson et al. 2012; Cuerda et al. 2014). Second-generation antipsychotics are frequently associated with weight gain (Allison et al. 1999; de Leon et al. 2007; Teff and Kim 2011; Teff et al. 2015), which might compromise patients' compliance (Tardieu et al. 2003), quality of life (Kruger et al. 2007), and metabolic and vascular status (Haupt and Newcomer 2002; Meyer et al. 2008). Frequently, this also might conduct patients to pharmacological discontinuation even if this is effective while putting them at risk of relapse (Zimmermann et al. 2003; Weiden et al. 2004). Among second-generation antipsychotics, olanzapine and clozapine are associated with much more severe antipsychotic-induced weight gain (AIWG) (Allison et al. 1999; Fernø et al. 2011; Milano et al. 2013; Cuerda et al. 2014; Lian et al. 2016).

Energy and weight regulation in the modern food environment is challenging (Chao et al. 2017), especially for those suffering from weight gain due to antipsychotics. AIWG is a problematic side effect and its etiological mechanism is still not fully understood (Allison et al. 1999; Cuerda et al. 2014). Based on the rapid effect of overeating and AIWG in severe mental illness (SMI) patients, it has been suggested that clozapine might induce central effects through gut-brain-hormones that would cause not only an increased appetite/decreased satiety but also specific food cravings (Brömel et al. 1998; Fernø et al. 2011). Clozapine effects on energy intake might over-ride the physiological counterregulation of some gut-brain-hormones related with appetite/satiety (e.g., leptin, adiponectin, ghrelin, and insulin), by modifying the expression of specific neuromodulators including orexigenic and anorexigenic neuropeptides (Fernø et al. 2011). Other lines of research in this field have relied on the receptor pharmacology model. According to this, olanzapine and clozapine share high affinities for 5-HT2C and histamine H1 receptors, while antagonize peripheral M3 muscarinic and central 5-HT2C receptors which might be related with hyperphagia increased weight gain and emergent diabetes in animal and human models (Tecott et al. 1995; Kroeze et al. 2003; Case et al. 2010; Teff and Kim 2011).

The concept of food craving and its biological pathway is not fully understood, either its assessments (Jáuregui Lobera et al. 2010). Some scales on food craving have been developed from a cognitive perspective, such as the Three Factor Questionnaire (TFQ) (Stunkard and Messick 1985). Others might involve specificity for different types of nutrients (Jáuregui Lobera et al. 2010), such as the Food Craving Inventory (FCI) (White et al. 2002).

Food craving has been classically defined as the intense urge or desire to eat a specific food (or type of food), as well as the difficulty of resisting to this urge (Weingarten and Elston 1990). Biologically, food craving for carbohydrates has been related to serotonin, a neurotransmitter which has also been linked to depression and obesity (Palacios et al. 2017). Following the model of addictions, food craving has also been associated with the dopamine/acetylcholine ratio in certain brain areas such as the nucleus accumbens (Hill et al. 1991; Gendall et al. 1997). Thus, the food craving and binge eating hypothesis has been proposed when explaining AIWG because of clozapine and olanzapine treatment (Theisen et al. 2003; Kluge et al. 2007), not being systematically investigated the role of appetite changes in SMI populations.

Previous food craving research on clozapine patients is limited to an open-label study in schizophrenic patients treated with clozapine (Brömel et al. 1998), a cross-sectional clozapine/olanzapine trial (Theisen et al. 2003), and a randomized double-blind study comparing clozapine and olanzapine (Kluge et al. 2007). However, differences in assessment methodology, food craving conceptualization, and the lack of nutrient specificity evaluation in these studies do not permit comprehensive comparisons between their results. Further, there is a lack of prospective studies focusing on clozapine-treated patients and food craving specificity.

Our primary objective has been to describe the longitudinal evolution of food craving in a sample of SMI patients starting clozapine treatment during an 18-week period of follow-up. Secondarily, authors aimed (1) to determine the relationship between anthropometric measures and the frequency of food cravings for different nutrients, (2) to assess if food craving changes might predict weight evolution in this sample, and (3) to examine the associations between food craving and self-reported habitual intake (consumption) of these foods.

Materials and methods

Patients

This study included 34 consecutively ascertained psychiatric patients with clinical indication to start clozapine treatment in the Hospital Clinic of Barcelona (Barcelona, Spain).

Inclusion criteria were wide to be considered close to clinical practice: (1) patients diagnosed from schizophrenia,

schizoaffective, or bipolar disorder according to the DSM-IV-TR criteria; (2) aged from 18 to 65 years old. The exclusion criteria were (1) history of traumatic brain injury and (2) mental retardation.

Each subject was informed of the purpose, procedures, and potential risks of participation in the study before signing an informed consent form. The protocol was approved by the local Ethical Committee and conducted in conformity with the Declaration of Helsinki.

Study design

Researchers conducted an observational prospective cohort study of 18 weeks of follow-up. A multidisciplinary team of two psychiatrist, two nurses, and one psychologist conducted the study procedures.

Because starting clozapine requires weekly blood monitoring due to its risk of agranulocytosis in the first 18 weeks and then monthly, study visits were linked to those at their regular clozapine care: (1) a baseline visit the previous week that clozapine was planned to start, (2) a week 8 treatment visit, and (3) a week 18 treatmen visit.

Clozapine was initiated with a dose of 12.5–25 mg in the first day of treatment, followed by weekly upward adjustments of 25–50 mg (i.e., standard titration). The titration was continued until satisfactory symptom control or development of major side effects according to clinical judgment. A complete weekly blood count, metabolic panel, clozapine and nor-clozapine plasma levels, and an electrocardiogram were obtained according to the regular monitoring on clozapine. All patients received standard hospi- tal care in the hospital and outpatient clinic in relation to clozapine monitoring.

Demographic, clinical, andanthropometric measures

Baseline visit included a complete set of demographic and clinical data via a questionnaire designed for this study. Most of the patients accomplished DSM-IV-TR (APA 2000) diagnostic criteria for schizophrenia (n = 27, 79.4%), followed by schizoaffective disorder and bipolar disorder patients (see Table 1).

Details of psychiatric clinical status with the use of the Positive and Negative Syndrome Scale (PANSS; Kay et al. 1987) and the Clinical Global Impression-Severity (CGI-S; Guy 2000) scale, as well as data on antipsychotic treat- ment, tobacco use, and previous presence of cardiovascular risk factors, were explored on the study visits by a trained staff.

Height, weight, and waist circumference were recorded for each patient, and BMI was calculated (BMI = weight [kg]/height^2 [m^2]). BMI status was determined according to the World Health Organization definition: BMI less than 18.5 kg/m^2, underweight; 18.5 to 25 kg/m^2, normal weight; 25 to 30 kg/m^2, overweight; and BMI 30 kg/m^2 or greater, obese (WHO 1995). Weight increase over 7% (Lieberman et al. 2005) and BMI status (normal weight (NW) vs overweight/obese (OWO)) were calculated in each critical study visit (baseline, week 8, and week 18).

Demographic, clinical, anthropometric measures, and food evaluations were recorded at baseline, week 8, and week 18 of follow-up.

Food questionnaires

Food Craving Inventory

Food craving was measured using the Food Craving Inventory-Spanish version (FCI-SP). This 28-item self-reported scale evaluates how often have you experienced craving for the food over the past month?^ It covers 28 Spanish sociocultural-adapted food types (Jáuregui Lobera et al. 2010). This defines craving as an intense desire to consume a particular food (or food type) that is difficult to resist.^ Participants rated how each food was craved over the past month on a 5-point Likert scale (from 1 (never) to 5 (always/almost every day)). FCI-SP presents a three-category structure: complex carbohydrates/proteins, simple sugars/trans fat, and saturated fats/high caloric content (fast food).

Its psychometric properties, internal consistency, and validity have been met in clinical psychiatric samples of non-psychotic outpatients (Jáuregui Lobera et al. 2010) while have proved acceptable internal consistency, reliability, and test-retest reliability in obese adults (Cronbach's alpha of 0.951) and healthy controls (Cronbach's alpha of 0.910) (Jáuregui Lobera et al. 2010).

Semi-quantitative food frequency questionnaire

The *Cuestionario de Frecuencia de Consumo de Alimentos* (CFCA) (Rodríguez et al. 2008) is a 45-item self-administered questionnaire elaborated to evaluate dietary habits (frequency of consumption; times per week/month) in th Spanish general population. The 45 items are grouped in 16 food categories: (1) meat, (2) sausages, (3) eggs, (4) fish, (5) milk, (6) dairy products, (7) cereals, (8) potatoes, (9) vegetables, (10) fruit, (11) sugars, (12) sugary drinks, (13) wine, (14) distilled beverages, (15) beer, and (16) light drinks. The CFCA has demonstrated acceptable reproducibility (Spearman's correlation from 0.49 to 0.75), better intra-class correlation (Spearman's correlation from 0.49 to 0.75), and correlation coefficients (varying from 0.41 to 0.67).

Statistical analysis

Descriptive statistics were used to present baseline demo- graphic, clinical, and anthropometric characteristics. Continues variables were expressed as me n and standard deviation (SD). Qualitative variables were presented as absolute frequency and percentage. These statistical analyses were performed by t test for independent groups and chi-square test, respectively.

Items from the FCI were compared with and matched to items from the CFCA (e.g., the FCI item indicating cravings for pizza was matched to consumption of pizza, patty, and croquette item in the CFCA) as it has been previously reported

Table 1 Descriptive characteristic s of the sample by BM I status

		BMI baseline status			*P* value
		NM (BMI< 25) *n* = 13 Mean (SD) or *N* (%)	OWO (BMI > 25) *n* = 21 Mean (SD) or *N* (%)	Total *n* = 34 Mean (SD) or *N* (%)	
Age, year		34.5 (11.4)	38.2 (12.8)	36.8 (12.2)	0.411†
Gender	Male	7 (53.9)	14 (66.7)	21 (61.8)	0.456*
	Female	6 (46.2)	7 (33.3)	13 (38.2)	
Early onset psychosis		4 (33.3)	15 (71.4)	19 (57.6)	0.033*
Time on antipsychotics, year		5.2 (7.6)	10.9 (11)	8.5 (10.1)	0.117†
Previous antipsychotic type	FGA	3 (23.1)	0 (0)	3 (8.8)	0.034*
	SGA	7 (53.8)	21 (100)	28 (82.4)	
	None	3 (23.1)	0 (0)	3 (8.8)	
Axis I diagnosis (DSM-IV-TR)	Schizophrenia	9 (69.3)	18 (85.7)	27 (79.4)	0.127*
	Schizoaffective	2 (15.4)	3 (14.3)	5 (14.7)	
	Bipolar disorder	2 (15.4)	0 (0)	2 (5.9)	
PANSS total		80.3 (9.5)	78.7 (23.1)	79.2 (19.3)	0.828†
CGI-S		5.1 (0.4)	4.4 (0.9)	4.7 (0.8)	0.016†
CV risk factors					
Smokers		9 (69.3)	5 (23.8)	14 (41.2)	0.009*
HTA		0 (0)	3 (14.3)	3 (9.1)	0.091*
CV illness		0 (0)	1 (4.8)	1 (3.1)	0.337*
DM		1 (8.3)	1 (4.8)	2 (6.1)	0.685*
Dyslipidemia		1 (8.3)	3 (14.3)	4 (12.1)	0.605*
Anthropometric measures					
Weight (kg)		63.3 (11.8)	90.9 (14.6)	80.9 (19.1)	< 0.001†
ΔWeight (kg)		6.3 (5.2)	0.2 (6.1)	2.3 (6.4)	0.012†
BMI (kg/m^2)		22 (2.7)	30.3 (3.7)	27.3 (5.3)	< 0.001†
ΔBMI (kg/m^2)		2.3 (1.9)	0.1 (2.0)	0.9 (2.2)	0.009†
Food craving evaluation					
FCI-total craving		2.4 (1.3)	2.5 (0.8)	2.4 (0.9)	0.831†
FCI-complex carbohydrates/proteins		2.3 (0.8)	2.6 (0.8)	2.5 (0.8)	0.448†
FCI-simple sugar /trans fat		2.6 (2.1)	2.3 (1)	2.4 (1.4)	0.594†
FCI-fast-food fats		2 (0.7)	2.7 (1)	2.5 (0.9)	0.067†

*χ^2 test

† Student *t*

Δ Increment after 18 weeks

BMI, body mass index; *CGI-S*, Clinical Global Impression-Severity; *CV*, cardiovascular; *DM*, diabetes mellitus; *FCI*, Food Craving Inventory; *FGA*, first-generation antipsychotic; *HTA*, hypertension; *NW*, normal weight; *OWO*, overweight-obesity; *PANSS*, Positive and Negative Syndrome Scale; *SD*, standard deviation; *SGA*, second-generation antipsychotic

(Chao et al. 2014). These items were used to form subscales that matched the FCI as closely as possible.

From those 34 patients initially included in the study, only 30 completed the visit at week 18. Lost of follow-up in one patient was due to change of catchment area (*n* = 1; 2.9%), clinical relapse (*n* = 2; 5.9%), and change of treatment because of adverse events (*n* = 1; 2.9%).

When evaluating longitudinal data, we firstly assessed time changes on weight after 18 weeks. Secondly, we analyzed longitudinal data on food craving scores (total and nutrient specific). Thirdly, we estimated the longitudinal association on weight change and food craving according to BMI status. For these analyses, we used generalized estimating equations (GEE) models, with an estimation of within-subject correlation from autoregressive approach (AR(1)). Results are expressed as estimated means and their 95% confidence intervals (95% CI). To explore the confounding effects of age, sex, early onset of psychosis, tobacco use, PANSS total baseline score, CGI-S baseline score, and baseline BMI, we individuallyadded these factors toeach model and studied changes in

the estimated regression coefficients (crude vs adjusted). Next, to explore to what extent BMI status modified the association between changes in weight and food craving, we added an interaction term to the model.

P value ≤ 0.05 was considered statistically significant, and all calculations were performed with SPSS ver. 25 (IBM) software. Due to the observational pragmatic nature characteristics of this study, no formal sample size calculation was performed and no methods for multiplicity were performed.

Results

Cross-sectional baseline analyses

Thirty-four patients were included in the study. Sample characteristics are presented in Table 1.

Mean sample age was 36.8 ± 12.2 years old. Fourteen patients (41.2%) were current smokers. Average BMI was 27.3 ± 5.3, being overweight the most common BMI classification (*n* = 11; 34.4%). When considering differences according to BMI status (NW vs OWO), there were more patients with a recent onset of psychosis (< 3 years) (*P* = 0.033) in the OWO group, and more severe (according to CGI-S) and smoker patients in the NW group (*P* = 0.016 and *P* = 0.009, respectively). No baseline differences were found, neither in total FCI craving.

Prospectivelongitudinal analyses at the 18th we k follow-up

Weight and BMI evolution

Of the total sample, 61.8% (*n* = 21) of the patients already started clozapine with a BMI greater than 25 (OWO), the 77.1% (*n* = 23) gained weight over 18 weeks of follow-up, and 37.9% (*n* = 11) gained more than 7% of weight at the end of the study period. Among individuals who gained weight, the average was 4.95 ± 3.71 kg.

Weight and BMI increased from baseline to week 18 of treatment (weight: − 2.25, 95% CI [− 4.44, − 0.07], *P* = 0.043; BMI: − 0.86, 95% CI [− 1.61, − 0.11], *P* = 0.025). When adjusting for covariates, gender, an early onset of psychosis, and the use of tobacco might explain weight increase after 18 weeks of treatment (Table 2). Stratified results according to BMI showed that weight increase was only significant in those NW (− 5.44, 95% CI [− 8.38, − 2.49], *P* < 0.001) after 18 weeks.

Food craving evolution: total and specific

Overall sample started clozapine treatment with a FCI total score of 2.4 (0.8) (2 = rarely, 3 = sometimes), with similar results for all specific nutrient cravings (Table 1). Crude longitudinal analysis did not show time differences in the FCI total craving score (− 0.01, 95% CI [− 0.32, 0.31], *P* = 0.949) while the assessment of potential confounders show how baseline BMI modified the effect of FCI total craving scores (0.04, 95% CI [0.01, 0.07], *P* = 0.009). The prospective specific food craving nutrient scores for the three studied categories (complex carbohydrates/proteins, simple sugar/trans fat, and fast-food fats) did not change over time in the crude models (− 0.21, 95% CI [− 0.51, 0.09], *P* = 0.161; 0.01, 95% CI [− 0.31, 0.32], *P* = 0.972; 0.20, 95% CI [− 0.19, 0.60], *P* = 0.319, respectively). However, the adjusted analyses of the FCI scores for fast-food fats showed how male gender (0.71, 95% CI [0.27, 1.14], *P* = 0.001) and baseline BMI (0.08, 95% CI [0.04, 0.12], *P* < 0.001) positively modify this association (Fig. 1).

Total food craving according to total FCI-SP craving and BMI status (NW vs OWO) When considering BMI status (NW vs OWO), the post hoc pairwise comparisons did not show neither intra-group nor between-group BMI status differences from baseline to week 18 (Table 3).

Complex carbohydrates/proteins craving according to FCI-SP specific score and BMI status (NW vs OWO) Intra-group differences among NW patients displayed a significant increase of ʙcomplex carbohydrates/proteinsˆ craving after 18 weeks of treatment in the NW group. These longitudinal differences were not found neither in the OWO group nor between the BMI groups (Table 3). The post hoc pairwise comparisons showed intra-group differences from baseline to 18 weeks of treatment in NW patients in relation to male gender (− 1.19; 95% CI [− 1.86, − 0.51]; *P* = 0.001), older age (− 0.67; 95% CI [− 1.10, − 0.24]; *P* = 0.002), tobacco use (− 0.94; 95% CI [− 1.47, − 0.42]; *P* < 0.001), recent onset of psychosis (− 1.03; 95% CI [− 1.24, − 0.83]; *P* < 0.001), and higher plasma levels of nor-clozapine (− 0.73; 95% CI [− 1.28, − 0.17]; *P* = 0.010). Neither age, nor gender, nor smoking habit, nor a recent onset of psychosis, nor higher levels of plasma nor-clozapine were found to be different through the study period in the OWO sample.

Simple sugar/trans fat craving according to FCI-SP specific score and BMI status (NW vs OWO) No intra-group or between-group differences through time were found in relation to the longitudinal evolution of the ʙsimple sugar/trans fatˆ nutrients craving (Table 3). On the post hoc pairwise comparisons, intra-group analyses were again just significant for the NW group from baseline to week 18. NW male patients (− 1.12; 95% CI [− 1.60, − 0.64]; *P* < 0.001), with old r age (− 0.48; 95% CI [− 0.73, − 0.23]; *P* < 0.001), tobacco use (− 0.63; 95% CI [− 1.12, − 0.15]; *P* = 0.010), recent onset of psychosis (− 1.20; 95% CI [− 1.47, − 0.93]; *P* < 0.001), and

Table 2 Longitudinal analysis of weight evolution at different study time-points

		NW (BMI < 25) $n = 13$		OWO (BMI > 25) $n = 21$		Total sample $n = 34$	
Model	Visit	EM (95% CI)	*P* value†	EM (95% CI)	*P* value†	EM (95% CI)	*P* value†
Crude	Baseline	62.2 (56.9; 69.6)*		90.9 (84.8; 96.9)		80.9 (74.5; 87.3)*	
	Week 8	66.8 (61.8;71.9)	0.013	91.2 (85.1; 97.2)	0.806	82.3 (76.4; 88.2)	0.101
	Week 18	68.7 (63.4; 73.9)	< 0.001	91.1 (85.3;96.8)	0.903	83.1 (77.7; 88.6)	0.043
Adj by age	Baseline	63.2 (56.8; 69.6)		90.9 (85.2; 96.7)		80.9 (74.5; 87.3)	
	Week 8	66.9 (91.8; 72.1)	0.011	91.2 (85.3; 97.1)	0.806	82.3 (76.4; 88.2)	0.103
	Week 18	68.8 (63.5; 74.1)	< 0.001	91.1 (85.4; 96.7)	0.919	83.1 (77.6; 88.5)	0.046
Adj by sex	Baseline	62.1 (57.1; 67.2)*		88.6 (83.5; 93.6)*		78.7 (72.9; 84.6)*	
	Week 8	66.2 (62.7; 69.6)	0.008	88.8 (83.9; 93.6)	0.807	80.2 (75; 85.)	0.102
	Week 18	68.4 (64.2; 72.6)	< 0.001	88.7 (83.9; 93.5)	0.897	81 (76.1; 85.9)	0.046
Adj by EOP	Baseline	62.8 (54.8; 70.7)		88.6 (83.9; 93.2)*		79.7 (74.1; 85.3)*	
	Week 8	66.8 (59.8; 73.7)	0.006	88.8 (84.4; 93.1)	0.807	81.3 (76.3; 86.2)	0.078
	Week 18	68.8 (61.2; 76.3)	< 0.001	88.7 (84.8; 92.7)	0.893	82.2 (77.7; 86.8)	0.026
Adj by smokers	Baseline	63.4 (56.6; 70.2)		90.3(85.5; 95.1)		79.6 (73.6; 85.5)*	
	Week 8	66.9 (61.7; 72.3)	0.017	90.5 (85.6; 95.4)	0.807	81 (75.6; 86.4)	0.107
	Week 18	68.8 (63.1; 74.5)	< 0.001	90.4 (85.7; 95.2)	0.910	81.8 (76.8; 86.8)	0.046
Adj by baseline PANSS	Baseline	59.2 (50.7; 67.6)		90.5(83.7; 97.2)		80 (71.7; 88.)	
	Week 8	62.7 (56.1; 69.5)	0.005	92.5 (85.6; 99.5)	0.010	82.7 (74.8; 90.5)	< 0.001
	Week 18	66.5 (59.1; 73.9)	< 0.001	92.2 (85.2; 99.2)	0.016	83.6 (76.2; 91)	< 0.001
Adj by baseline CGI_S	Baseline	59.1 (51.5; 67.1)		90.4 (83.9; 96.8)		79.9 (71.8; 88)	
	Week 8	62.7 (56.4; 69.1)	0.005	92.4 (85.6; 99.2)	0.010	82.6 (74.9; 90.4)	< 0.001
	Week 18	66.4 (59.4; 73.4)	< 0.001	92.1 (85.2; 98.9)	0.016	83.6 (76.3; 90.9)	< 0.001

*Significant *P* values as covariates (< 0.05)

† Reported *P* values from baseline

CI, confidence interval; *EM*, estimated means

higher values of nor-clozapine plasma levels (− 0.61; 95% CI [− 1.21, − 0.01]; $P = 0.046$) were found to be associated with higher values of this specific food craving after 18 weeks of treatment. Again, neither age, nor gender, nor smoking habit, nor a recent onset of psychosis, nor higher levels of plasma nor-clozapine were found to be different through the study period in the OWO sample.

Fast-food fats craving according to FCI-SP specific score and BMI No intra-group differences were found, but baseline between-group differences appeared. Baseline scores were significantly higher in the OWO group in comparison with the NW patients(NW: 2.05, 95% CI [1.60, 2.49]; OWO: 2.81, 95% CI [2.37, 3.25]; $P = 0.016$) (Table 3).The post hoc analysis showed that at baseline and at week 18 of treatment, NW male patients were statistically associated with a higher ʙfast-food fats^ craving score in comparison with female NW (baseline: − 0.92, 95% CI [− 1.81, − 0.03], $P = 0.042$; week 18: − 1.76, 95% CI [− 2.64, − 0.88], $P < 0.001$). These gender differences were not found in the OWO sample. According to age, smoking, a recent onset of psychosis, andnor-clozapine plasma levels, no differences were found neither in the NW nor in the OWO patients through time. However, at week 18 of treatment, those OWO patients with a recent onset of psychosis presented higher values of this craving in comparison with the OWO without a recent onset of psychosis (− 0.59, 95% CI [− 1.08, − 0.09], $P = 0.019$).

Weight and food craving evolution

To address the question whether weight increase on clozapine-treated patients would predict changes in food craving (total and nutrient specific), new GEE analyses included baseline BMI since it seems to modify the longitudinal results of the food craving score (as shown in the ʙResults^ section). Thus, the interaction term time*BMI (BMI status) was included in the model. Changes in total FCI scores, ʙcomplex carbohydrates/proteins^ FCI scores, and ʙsimple sugar/trans fat^ FCI scores were not associated with weight increase after 18 weeks of clozapine (β = − 4.89 ± 2.55, 95% CI [− 9.88, 0.11], $P = 0.055$; β = − 3.44 ± 3.19, 95% CI [− 9.69, 1.16], $P = 0.281$; β = 0.43 ± 5.20, 95% CI [− 9.76, 10.63], $P = 0.934$, respectively). However, ʙfast-food fats^ FCI score changes

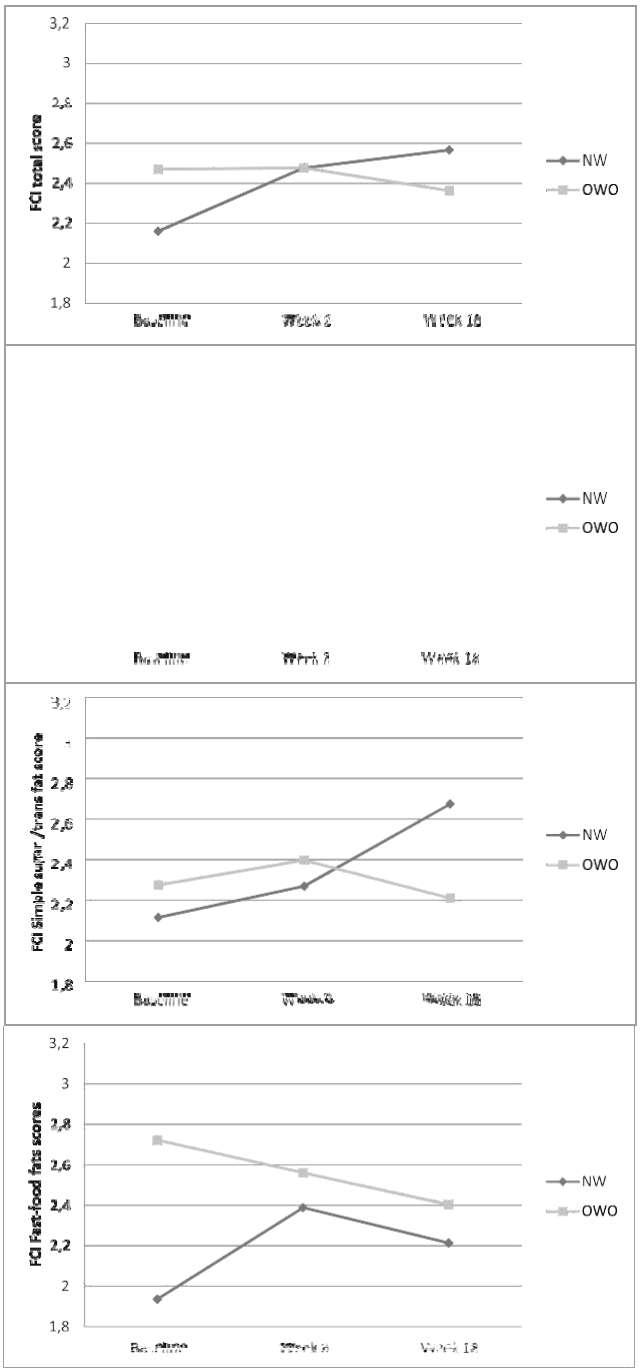

Fig. 1 FCI (total and nutrient specific) mean scores in BMI subgroups at different study visits. FCI: Food Craving Inventory; NW: normal weight; OWO: overweight-obesity

predicted weight increase from baseline (β = − 5.35 ± 1.67, 95% CI [− 8.64, − 2.06], *P* = 0.001).

Food craving evolution and food consumption

When modeling the change after 18 week of clozapine treatment in the different FCI-SP specific food scores with the change in frequency of food equivalent consumption (through the CFCA specific score), changes in the three different FCI-SP craving scores evaluated were positively associated with changes in the equivalent three CFCA specific scores: FCI-CFCA for ʙcomplex carbohydrates/proteins^ (β = 0.03 ± 0.01, 95% CI [0.01, 0.05], *P* = 0.001); FCI-CFCA for ʙsimple sugar/trans fat^ (β = 0.03 ± 0.01, 95% CI [0.02, 0.05], *P* < 0.001); FCI-CFCA for ʙfast-food fats^ (β = 0.07 ± 0.02, 95% CI [0.03, 0.11], *P* < 0.001).

Discussion

Our results did not find any longitudinal change in food craving when evaluating the total sample. However, when considering the BMI status (NW vs OW) in each study point, intra-group differences in the NW group about how ʙcomplex carbohydrates/proteins^ FCI-SP craving scores increase were detected. After controlling for potential confounding factors, both specific FCI scores showed that male gender, older age, smoking habit, recent onset of psychosis, and higher values of nor-clozapine plasma levels were associated with a longitudinal increase of those specific cravings in the NW group. However, our research did not achieve statistical significance in finding between-group longitudinal differences in the diverse food craving assessments according to the BMI status group. Thus, when exploring if weight increase might be predicted by changes in food cravings, only those changes related with ʙfast-food fats^ were significant. Yet, to our knowledge, this is the first prospective naturalistic study in a sample of SMI patients that starts treatment with clozapine with an extended evaluation of food craving and consumption in terms of nutrient specificity. Indeed, we used specific statistical models to test the longitudinal evolution of food craving (total and specific) after staring treatment with clozapine for 18 weeks.

Regarding ʙfast-food fats^ FCI-SP craving score, despite the OWO group presented higher values at baseline, no longitudinal differences were found over time, even when associated confounding factors were tested in the model. Nevertheless, it seems that longitudinal evolution in this specific food craving might predict weight increase due to clozapine in this sample. It has been previously described in community-based samples without mental illness that OWO individuals tend to present igher presence of food craving and consumption than NW people (Abilés et al. 2010; Chao et al. 2014, 2017). Thus, it is still uncertain if those are specific for any kind of food. At least, in our sample, baseline results suggest that OWO patients present higher craving for this subtype of food. This specificity of findings has never been tested before through these scales on SMI patients. Results from a cross-sectional non-psychiatric community-based sample (*n* = 646) that used the FCI scale to describe associations between specific food cravings, food intake, and BMI status showed significant relationships between the different subtypes of food craving with higher BMI after immediate food intake (Chao et al. 2014). However, the

Table 3 Longitudinal analysis of weight evolution at different study timepoints and according to BMI status

	Baseline		Week 8		Week 18	
	Mean	95% CI	EM	95% CI	EM	95% CI
FCI - total craving score						
NW	2.19	[1.73, 2.66]	− 0.93	[− 0.66, 0.45]	− 0.44	[− 1.09, 0.21]
From baseline, *P* value				0.783		0.185
OWO	2.51	[2.16, 2.86]	0.63	[− 0.26, 0.39]	0.16	[− 0.15, 0.47]
From baseline, *P* value				0.698		0.311
Between groups, *P* value	0.285		0.542		0.297	
FCI - complex carbohydrates/proteins						
NW	2.45	[1.91, 2.98]	− 0.23	[− 0.91, 0.43]	− 0.67	[− 1.15, − 0.19]
From baseline, *P* value				0.485		0.010
OWO	2.62	[2.28, 2.96]	0.88	[− 0.24, 0.42]	− 0.08	[− 0.42, 0.25]
From baseline, *P* value				0.595		0.640
Between groups, *P* value	0.608		0.680		0.192	
FCI - simple sugar/trans fat						
NW	2.21	[1.75, 2.66]	0.06	[− 0.34, 0.47]	− 0.44	[− 0.98, 0.11]
From baseline, *P* value				0.758		0.113
OWO	2.29	[1.83, 2.75]	− 0.05	[− 0.39, 0.29]	0.13	[− 0.22, 0.48]
From baseline, *P* value				0.788		0.458
Between groups, *P* value	0.785		0.303		0.059	
FCI - fast-food fats						
NW	2.05	[1.60, 2.49]	− 0.21	[− 0.93, 0.51]	− 0.31	[− 1.09, 0.47]
From baseline, *P* value				0.562		0.435
OWO	2.81	[3.37, 3.25]	0.24	[− 0.18, 0.66]	0.42	[− 0.01, 0.85]
From baseline, *P* value				0.262		0.054
Between groups, *P* value	*0.016*		0.476		0.926	

FCI, Food Craving Inventory; *NW*, normal weight; *OWO*, overweight-obesity

naturalistic follow-up of this sample after 6 months did not show association between the different food cravings and BMI evolution (Chao et al. 2017).

When analyzing the total FCI craving scores according to the BMI patient status (NW vs OWO), results failed in finding longitudinal differences. These results were also contradictory to previous reported literature on the field, where an increase on total food craving was found (Brömel et al. 1998; Theisen et al. 2003; Kluge et al. 2007). However, differences in assessment methodology, the small samples sizes, and conceptualization of food craving might not permit an optimal association of results between them. In the case of the open-labe study of 12 schizophrenic patients treated with clozapine, Brömel et al. (1998) used a semi-structured questionnaire of appetite/hunger related to AIWG and leptin plasma levels. Later, a cross-sectional trial of clozapine vs olanzapine that aimed to evaluate eating behavior in a sample of adolescents and young adults with psychotic disorders ($n = 74$) found that both, olanzapine and clozapine, presented an increase of binge eating behavior (Theisen et al. 2003). A more recent randomized double-blind trial that evaluated food craving in a sample of psychotic disorder patients ($n = 30$) comparing clozapine vs olanzapine found that olanzapine patients experienced higher levels of food craving in comparison with clozapine-treated patients (Kluge et al. 2007).

Our findings also highlight that, in the different types of food craving, there was a longitudinal association with the self-reported habitual intake of these foods. Again, this relation has not been previously explored on SMI patients. However, Chao et al. (2014) positively correlated all different kinds of FCI cravings with their respective food intake in community-based studies. With this, our findings extent prior knowledge on non-psychiatric samples, suggesting that food craving and consumption are significant related constructs (Martin et al. 2008; Chao et al. 2014) and AIWG in SMI populations could be also quantified with self-reported measuring scales of food craving and consumption.

Overall, on the NW group, FCI and BMI status longitudinal differences might rely on the possibility that NW and OWO weight patients compensate for food craving and intake by different mechanisms to maintain their weight (e.g., reducing caloric intake or increasing physical activity). It is also possible that OWO patients underreport their food intake. A longitudinal

increased craving profile in the NW subgroup has been described in our study as males, older, a recent onset of psychosis (which could mean less years of antipsychotic burden), smokers, and with higher nor-clozapine plasma levels (which might relate a plasma concentration effect). Thus, in our sample, there were more smokers among the NW group, making it difficult to interpret this profile due to the controversial literature regarding smoking and food craving. Besides smoking has been associated with obesity-related behaviors (e.g., unhealthy diet), it has been also considered as reducing appetite and increasing satiety in non-SMI populations (Chiolero et al. 2006), while it has been also proposed that there is a cross-substance craving among smokers (Audrain-McGovern and Benowitz 2011). Indeed, the NW sample, which craved more for the ʙcomplex carbohydrates/proteins,ˆ presented a unique profile to target interventions.

There are several limitations to mention in this study. While the effect sizes of the findings were small, it is important to note that we studied the natural course and outcome of a specific pragmatic clinical sample. Results maynot generalize to other groups. Firstly, our results included a prospective short-term (18 weeks) follow-up assessment for predicting future food cravings and weight gain. The longer-term effects of clozapine treatment on food craving preferences and their associated weight outcomes are unknown and longer follow-up studies are needed. Secondarily, the validity of subjective reports on food craving and consumption measured with the FCI-SP and CFCA should be also matched with cognitive performance and might be subject to recall and response biases. Thirdly, we compared cravings for specific types of foods with intake of these categories of food. It is possible that some food cravings may be quite specific to the individual food item rather than an entire food class. Fourthly, it is also possible that cravings are a conditioned phenomena: people maycrave the foods that they frequently eat.

Taking together our findings, it could be suggested that dietary interventions in SMI settings should benefit from the evaluation of longitudinal craving and consumption in order to develop more individualized interventions, especially in those starting obesogenic antipsychotics as NW.

Conclusions

The results of this study suggest that there is a significant relationship between BMI status (NW patients) and food cravings, that specific food craving for ʙfast-food fatsˆ might predict weight gain, and that there is a positive correlation between craving and consumption of these types of foods.

A more comprehensive understanding of the role of appetite changes in AIWG would be helpful to clinicians and patients; some of whom report substantially increased appetite starting after their first dose of an antipsychotic (Case et al. 2010). Accurate evaluations to detect changes in appetite might provide early warning signs of AIWG risk as well as information for adequate treatment choices, especially in those that started clozapine treatment being NW. If specific changes in appetite can be expected, patients can be informed in advance and may be better able to manage them (Case et al. 2010). Another area that needs to be explored by further research is the potential changes in gut-brain hormones and gut microbiota after treatment with clozapine or other antipsychotics (Salagre et al. 2017).

To succeed in the holistic treatment of schizophrenia, the AIWG side effect requires to be mitigated. For this, future research needs to test whether intervention targeting food preferences may help to soften weight gain in patients starting treatment with clozapine.

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Authors' contribution MG: conception and design of the article, acquisition, analyses, and interpretation of data, and drafting the manuscript. AM: conception and design of the article, acquisition, and interpretation of data, revising critically for contents. LS: conception and design of the article, acquisition, and interpretation of data, revising critically for contents. JR: analyses, interpretation of data, and revising critically for contents. MS: analyses, interpretation of data, and revising critically for contents. EP: revising the manuscript critically for intellectual content and approved the final version of the manuscript. MGR: analyses, interpretation of data, and revising critically for contents. CO: revising the manuscript critically for intellectual content and approved he final version of the manuscript. SA: acquisition and interpretation of data, revising critically for contents. EV: revising the manuscript critically for intellectual content and approved the final version of the manuscript. MB: revising the manuscript critically for intellectual content and approved the final version of the manuscript. CGR: conception and design of the article, revising the manuscript critically for intellectual content, and approved the final version of the manuscript.

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Compliance with ethical standards

The protocol was approved by the local Ethical Committee and conducted in conformity with the Declaration of Helsinki.

Conflict of interest Marina Garriga has received grants and served as consultant or advisor for Ferrer, Lundbeck, Janssen, Spanish Ministry of Economy and Competitiveness, Instituto de Salud Carlos III through a 'Rɪo Hortega' contract (CM17/00102), FEDER, and Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM).

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Antipsychotic-Associated Weight Gain and Clinical Improvement Under Clozapine Treatment

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Abstract:

Background: Antipsychotic-associated weight gain is a common adverse effect with several negative outcomes in the clinical evolution of patients, which might also affect patients' self-identity from physical appearance and imply treatment discontinuation. However, recent research has drawn atten - tion to an unexpected clinical improvement associated with weight gain, mostly in patients under treatment with clozapine or olanzapine.

Methods: Twenty-three treatment-resistant psychosis patients initiating clozapine were evaluated. Longitudinal psychopathological assessment through the Positive and Negative Syndrome Scale (PANSS) and anthropometric evaluation were performed at baseline, week 8, and 18.

Results: Body mass index (BMI) changeduring clozapine treatment was associated with clinical improvement measured with PANSS total score at week 8 ($P = 0.021$) while showed a trend at week 18 ($P = 0.058$). The PANSS general score was also associated with weight gain at week 8 ($P = 0.022$), whereas negative subscale score showed a trend at week 8 ($P = 0.088$) and was associated between week 8 and 18 ($P = 0.018$). Sex differences applied at week 8 for PANSS total score, where clinical improvement was significantly associated with BMI in male subjects ($P = 0.024$). We also stratified for time to initiate clozapine, finding significant associations in negative symptom at week 8 ($P = 0.023$) and week 18 ($P = 0.003$) for subjects, which started clozapine after 3 years of illness.

Conclusions: Our results suggest that in subjects initiating clozapine, clinical improvement is associated with BMI increase, mostly in negative symptom and in patients after 3 years of antipsychotic use. Our findings were already described in the preantipsychotic era, suggesting some pathophysiological mechanism underlying both conditions.

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"Das Körpergewicht Zeigt Namentlich Bei den akuten Formen häufigganz unregelmäßige und starke Schwankungen, für die man keinen Grund kennt"

Eugene Bleuler "Dementia praecox oder die Gruppe der Schizophrenien."

"In acute forms of the illness the patient's weight in particular is often subject to irregular and wide variations for which there is no known explanation"

Eugene Bleuler "Dementia Praecox or the group of schizophrenias."

Antipsychotic-associated weigh gain (AIWG) is a common adverse effect during acute and maintenance treatment affecting up to 72% of patients.[1] Despite its metabolic consequences,[2] it increases the risk of treatment discontinuation thorough subjective distress from weight gain.[3] It also affects self-identity from physical appearance, a findingalready highlighted in first-episode patients.[4] Indeed, it is also a major concern for caregivers[5] that clozapine is one of the antipsychotics more related to AIWG[6] and leads to laxative overuse.[7]

Recent research has drawn back attention to the possible effect of AIWG and clinical improvement.[8,9] Surprisingly, most of the studies are focused on clozapine (and olanzapine) treatment, antipsychotics highly related with AIWG.[10] However, descriptions from the preantipsychotic era already related weight change with clinical improvement or worsening. Eugene Bleuler in his book "*Dementia praecox oder die Gruppe der Schizophrenien*" describedthat "rapid weight gain without a corresponding improvement in the patient's mental state has always been considered a sign of poor prognosis in acute psychoses."[11] Later seminal studies confirmed previous suspicions, as weight gain related with phenothiazide treatment (chlorpromazine) was associated with behavioral improvement.[12] However, this association has remained forgotten until the early 90s, when new research was conducted in patients under clozapine treatment.[13-19] These previous studies suggested clinical improvement associated with weight gain over time, but other authors did not confirm this association.[20-22]

A recent systematic review has summarized and confirmed the unexpected association[8] while discussing the potential role of confounders such as type of antipsychotic medication, compliance, duration of the treatment, previous antipsychotic exposure, or baseline anthropometry and psychopathology. Although weight gain due to antipsychotics has been widely reported on the first weeks of antipsychotic treatment, there is no further evidence on durationof treatment beinga critical factor mediatingtheassociation

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between AIWG and therapeutic improvement.[8] Indeed, another novel systematic review and network meta-analysis with 18 different antipsychotics retrieved back the concept from a different perspective. Authors suggested that more efficacious antipsychotics, such as olanzapine and clozapine, are generally associated with weight gain; however, they do not intend to justify that metabolic disturbance is required for efficacy but to highlight that its association might be due to off-target actions.[10] Nevertheless, clozapine nowadays is underused,[23] with many different strategies worldwide aimed at improving its utilization according to the ratio of treatment-resistant schizophrenia, improving its prescription at initial stages of the disease.[24]

Thus, although clozapine is the most effective antipsychotic medication for treatment-resistant schizophrenia[25,26] and it is well known that delayed initiation of clozapine may be related to poor clinical psychotic response,[27] there is a long delay in initiating clozapine during routine clinical practice.[27] For this reason, initiating clozapine in the initial 3 years of evolution might improve symptomatic outcomes and prevent clozapine-resistant schizophrenia,[28] because delayed initiation beyond the 3 years of illness might imply worse clinical outcomes.[28,29]

With the previous rationale, we aim to evaluate the potential association between clinical improvement due to clozapine treatment and anthropometric change over time in a cohort of patients initiating clozapine treatment due to resistant psychosis. As secondary objectives, we intend to assess sex differences on this potential association as well as the importance of early versus delayed use of clozapine.

MATERIAL AND METHODS

Study Design

Thirty-six patients were recruited from an analytic, observational prospective study of 18 weeks of follow-up.[30] Patients were recruited from the acute ward (n = 6, mean length hospital of 18.5 days) or the dayhospital (n = 14) or the outpatients (n = 16) clinics associated with Hospital Clinic of Barcelona. Twenty-three patients ended the follow-up with reliable longitudinal data, so longitudinal analyses were based on this subsample (7 were dropouts and 6 patients had missing longitudinal required data). A multidisciplinary team of 2 psychiatrist, 2 nurses, and 1 psychologist conducted the study procedures. Each subject was informed of the purpose, procedures, and potential risks of participation in the study before signing an informed consent form. The protocol was approved by the local ethical committee and conducted in conformity with the Declaration of Helsinki. Three study visits were performed: at baseline, at week 8, and week 18 of treatment. All patients received a standard clinical care, complete blood count, metabolic evaluation, and an electrocardiogram, which were obtained according to the regular monitoring on clozapine.

Study Procedures and Data Collection: Demographic, Clinical, Physical, and Anthropometric Measures

Baseline visits included a complete set of demographic and clinical data. All subjects were clinically interviewed using the Spanish translation of the Structured Clinical Interview for *Diagnostic and Statistical Manual of Mental Disorders*, *Fourth Edition*, Axis I Disorders.[31] Clinical baseline assessment was recorded using preplanned structured interviews, which included a review of the current medical and psychiatric history, clinical and sociodemographic variables, and history of previous prescribed medication if proper.

Psychopathological assessment with the Positive and Negative Syndrome Scale (PANSS)[32] was performed at baseline, weeks 8, and 18. Height, weight, and waist circumference were measured for each patient and body mass index (BMI) was calculated (BMI = weight [in kilograms] / height^2 [in square meters]).

Clozapine oral dosages were recorded at each study visit to be considered of interest in relation to weight gain. Clozapine and norclozapine blood levels were performed (measured at week 8 and week 18). Norclozapine has been shown to have higher antagonist activity at $5HT_{1c}$, $5\text{-}HT_{2C}$, and $D_{1,2}$ receptors with additional activity as an M_1-muscarinic partial agonist suggesting a pathophysiological pathway for increased clozapine-associated weight gain.[33]

Duration of treatment was calculated as the time since the first antipsychotic treatment until the introduction of clozapine and patients were later stratified according to the early (less than 3 years of antipsychotic treatment) or delayed (more than 3 years of treatment) introduction of clozapine.

Statistical Analysis

Descriptive statistics were used for demographic, clinical, and anthropometric variables. Continues variables were expressed as mean and standard deviation (SD). Qualitative variables were presented as absolute frequency and percentage. These statistical analyses were performed by *t* test for independent groups and x^2 test respectively.

General Lineal Model analyses were conducted for each time frame. Analyses from baseline to week 8 included adjusted models assessing the psychopathological status evaluated with the PANSS scale (positive, negative, general, and total subscores) at week 8 and were adjusted by age, sex, PANSS corresponding subscale at baseline, anthropometric difference between 8 and baseline (according to BMI), and norclozapine levels at week 8. On week 18 analyses, the dependent variable was the PANSS (positive, negative, general, and total subscores), but at week 18, and the independent variables were: age, sex, PANSS corresponding subscales at week 8, anthropometric difference between week 18 and week 8 (according to BMI), and norclozapine value difference between week 18 and week 8.

To answer the secondary aims of this study, the sample was later stratified firstly, according to sex and later in between subjects, which have started clozapine early (in their first 3 years since the initial antipsychotic treatment) or delayed (after). Sex was not included on this later analysis because of the small sample size. A P value ≤ 0.05 was considered statistically significant, and all calculations were performed with SPSS ver. 25 (IBM) software.

RESULTS

Psychopathological Improvement and Weight Impairment Association Through the Follow-up

A total of 36 patients were recruited from an analytic, observational prospective study of 18 weeks of follow-up and 23 patients ended the follow-up.

A summary of demographic, clinical, and psychopathological baseline assessments is shown in Table 1, for the overall sample and for stratified subsamples depending on early or delayed introduction on clozapine (Table 1).

The General Lineal Model analyses that were applied to investigate the combined effect of clinical improvement and weight impairment (according to BMI evolution) were realized at 2-time sets (Table 2).

At week 8 of clozapine treatment, it was found that the PANSS total score was associated with BMI increase from baseline

TABLE 1. Demographic, Clinical, and Psychopathological Baseline Assessments for the Overall Sample and Stratified Differences According to Early (First 3 Years of Treatment) and Delayed Use of Clozapine (After 3 Years of Treatment)

		Total Sample (N = 23)	Early use Clozapine (<3 y, n = 9)	Delayed Use Clozapine (>3 y, n = 14)	*P*
Mean (SD) or n (%)					
Age, y		37.05 (12.67)	28.18 (8.19)	42.74 (11.87)	0.004*
Sex	Female	10 (44)	6 (66)	4 (28)	0.086
Axis I diagnoses (*DSM-IV-TR*)	Schizophrenia	20 (87)	8 (88.9)	12 (85.7)	0.705
	Schizoaffective	2	0	2 (14.3)	
	Bipolar disorder	1	1 (11.1)	0	
Psychopathological assessment					
PANSS total		78.87 (20.25)	74.00 (17.97)	82.00 (21.63)	0.367
PANSS positive		19.04 (7.62)	19.11 (9.54)	19.00 (6.49)	0.111
PANSS negative		22.39 (6.79)	20.44 (5.45)	23.64 (7.43)	0.280
PANSS general		37.43 (9.92)	34.44 (8.27)	39.36 (10.68)	0.256
PSP		51.04 (14.18)	51.78 (13.45)	50.57 (15.12)	0.848
Anthropometric measures					
BMI, kg/m^2		27.66 (5.35)	23.58 (4.71)	30.28 (3.97)	0.001*
Weight, kg		81.23 (18.08)	67.17 (14.14)	90.25 (14.34)	0.001*

*$P < 0.05$.
DSM-IV-TR: Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision; PSP, personal and social performance.

($P = 0.021$), baseline PANSS total score ($P < 0.001$), age ($P = 0.041$), and sex ($P = 0.024$), whereas norclozapine levels at week 8 were not ($P = 0.413$). For the PANSS negative subscale at week 8, BMI increase from baseline only showed a trend ($P = 0.088$) being associated with baseline PANSS nega-tive subscore ($P < 0.001$) and age ($P = 0.029$), whereas sex($P = 0.206$) and norclozapine levels at week 8 were not($P = 0.578$). For the PANSS general subscale at week 8, BMI increase from baseline ($P = 0.022$) and baseline PANSS generalsubscore ($P < 0.001$) were significantly associated, whereas age($P = 0.235$), sex ($P = 0.121$), and norclozapine levels at week 8were not ($P = 0.281$). At week 18, for the PANSS total score, BMI increase only showed a trend toward signification ($P = 0.058$)on this second period of study observation, whereas PANSS totalscore at week 8 ($P = 0.108$), age ($P = 0.513$), sex ($P = 0.380$),and norclozapine levels at week 18 ($P = 0.818$) were not associated.For the PANSS negative subscale, BMI increase ($P = 0.018$) and PANSS negative subscore at week 8 ($P = 0.003$) were significantly associated, whereas age ($P = 0.606$), sex ($P = 0.807$), and norclozapine levels at week 18 ($P = 0.784$) were not.

Clozapine Introduction Differences on the Association Between Psychopathological Improvement and Weight Impairment

No differences on clinical assessments were found at baseline according to the moment where clozapine was introduced besides those that started clozapine early, presented less weight (and BMI) that those starting clozapine after 3 years (Table 1).

When stratified by years of treatment until the initiation of clozapine, we found out that in patients who started clozapine within the first 3 years, no significant association was found between BMI increase and changes on the psychopathology (at any subscore or total PANSS score). A trend toward significancewas detected at week 8, where negative symptom (PANSS nega-tive score) was associated with BMI increase ($P = 0.061$). How-ever, when considered patients whose clozapine was started after 3 years of treatment, a significant association was detected between negative symptom (PANSS negative score) at both, week 8 and week 18. At week 8, for the PANSS negative subscale, baseline PANSS negative subscale ($P < 0.001$) and BMI increase ($P = 0.023$) were significantly associated, whereas age ($P = 0.109$) and norclozapine levels ($P = 0.684$) were not. At week 18, for the PANSS negative subscale, PANSS negative subscale at week 8 ($P = 0.014$) and BMI increase ($P = 0.003$) were significantly associated, whereas age ($P = 0.638$) and changes in norclozapine levels from week 8 to 18 ($P = 0.485$) were not (Table 2).

DISCUSSION

In our sample of 23 patients diagnosed with treatment-resistant psychosis (schizophrenia, schizoaffective psychosis, and bipolar disorder), initial significant associations were found between clinical improvement in the total PANSS score and general psychopathology subscores and BMI increase over the first 8 weeks of clozapine treatment, whereas in the PANSS negative subscore, there was a trend toward significance. Nevertheless, between week 8 and 18, increases on BMI were significantly associated with clinical improvement according to the PANSS negative subscale score while showing a trend in PANSS total score.

Clinical improvement evaluated with PANSS total score was significantly associated at week 8 and showed a trend at week 18. Similar results were found on a sample of 38 patients where a significant inverse association between BMI and PANSS total over 14 weeks of follow-up was described.[15] On another sample of 74 patients, BMI was a significant predictor of total psychopathology evaluated with the Brief Psychiatric Rating Scale.[14] In addition, in a sample of 15 patients, it was described a pattern of clinical improvement while increasing weight gain followed by subsequent stability.[16] Another important finding also emerged, negative symptom evaluated with the PANSS negative subscale, was significantly associated with BMI mean increase between week 8 and 18, while showing a trend toward significance on the baseline to week 8 assessment. Similar results were described in a longitudinal study evaluated by the scale of assessment of negative symptoms[14] and ina transversal studyevaluated withthe Brief Negative Symptom Scale.[34]

TABLE 2. General Lineal Model Analyses at Week 8 and Week 18 of Clozapine Treatment Stratified by Time of Clozapine Initiation

	PANSS Subscore		ΔBMI		Age		ΔNorclozapine	
	Week 8	Week 18	Week 8	Week 18	Week 8	Week 18	Week 8	Week 18
PANSS total								
Early CLZ	57.78 (10.58) $F = 12.96$; $df = 1$ $P = 0.011$*	54.33 (12.93) $F = 0.00$; $df = 1$ $P = 0.981$	24.55 (2.55) $F = 1.80$; $df = 1$ $P = 0.228$	25.04 (2.91) $F = 0.19$; $df = 1$ $P = 0.687$	$F = 7.08$; $df = 1$ $P = 0.037$*	$F = 0.73$; $df = 1$ $P = 0.442$	73.33 (43.33) $F = 0.57$; $df = 1$ $P = 0.478$	84.88 (61.51) $F = 0.00$; $df = 1$ $P = 0.989$
Delayed CLZ	68.43 (14.69) $F = 72.27$; $df = 1$ $P < 0.001$*	60.14 (13.27) $F = 8.28$; $df = 1$ $P = 0.024$*	30.93 (4.30) $F = 4.67$; $df = 1$ $P = 0.068$	31.28 (4.20) $F = 5.44$; $df = 1$ $P = 0.052$	$F = 0.15$; $df = 1$ $P = 0.710$	$F = 0.02$; $df = 1$ $P = 0.899$	126.08 (99.38) $F = 1.88$; $df = 1$ $P = 0.213$	161.50 (101.14) $F = 0.66$; $df = 1$ $P = 0.442$
PANSS positive								
Early CLZ	13.33 (5.85) $F = 22.97$; $df = 1$ $P = 0.003$*	12.22 (6.12) $F = 0.72$; $df = 1$ $P = 0.444$	$F = 0.36$; $df = 1$ $P = 0.567$	$F = 0.48$; $df = 1$ $P = 0.527$	$F = 0.07$; $df = 1$ $P = 0.799$	$F = 0.14$; $df = 1$ $P = 0.727$	$F = 5.03$; $df = 1$ $P = 0.654$	$F = 0.02$; $df = 1$ $P = 0.908$
Delayed CLZ	15.00 (4.00) $F = 102.59$; $df = 1$ $P < 0.001$*	12.64 (3.48) $F = 8.22$; $df = 1$ $P = 0.024$*	$F = 0.02$; $df = 1$ $P = 0.895$	$F = 0.51$; $df = 1$ $P = 0.500$	$F = 3.17$; $df = 1$ $P = 0.118$	$F = 0.51$; $df = 1$ $P = 0.865$	$F = 3.47$; $df = 1$ $P = 0.105$	$F = 0.07$; $df = 1$ $P = 0.794$
PANSS negative								
Early CLZ	16.67 (5.32) $F = 30.71$; $df = 1$ $P = 0.001$*	14.78 (4.79) $F = 2.12$; $df = 1$ $P = 0.219$	$F = 5.29$; $df = 1$ $P = 0.061$	$F = 0.05$; $df = 1$ $P = 0.836$	$F = 15.47$; $df = 1$ $P = 0.008$*	$F = 1.19$; $df = 1$ $P = 0.237$	$F = 5.03$; $df = 1$ $P = 0.066$	$F = 0.06$; $df = 1$ $P = 0.674$
Delayed CLZ	20.43 (6.81) $F = 90.68$; $df = 1$ $P < 0.001$*	18.79 (6.84) $F = 10.72$; $df = 1$ $P = 0.014$*	$F = 8.43$; $df = 1$ $P = 0.023$*	$F = 19.87$; $df = 1$ $P = 0.003$*	$F = 3.38$; $df = 1$ $P = 0.109$	$F = 0.24$; $df = 1$ $P = 0.638$	$F = 0.18$; $df = 1$ $P = 0.684$	$F = 0.54$; $df = 1$ $P = 0.485$
PANSS general								
Early CLZ	27.78 (4.27) $F = 7.04$; $df = 1$ $P = 0.038$*	27.33 (5.03) $F = 0.02$; $df = 1$ $P = 0.898$	$F = 0.00$; $df = 1$ $P = 0.952$	$F = 0.00$; $df = 1$ $P = 0.952$	$F = 5.07$; $df = 1$ $P = 0.065$	$F = 0.17$; $df = 1$ $P = 0.704$	$F = 0.09$; $df = 1$ $P = 0.778$	$F = 0.00$; $df = 1$ $P = 0.994$
Delayed CLZ	33.00 (7.13) $F = 38.50$; $df = 1$ $P < 0.001$*	28.57 (5.54) $F = 13.44$; $df = 1$ $P = 0.008$*	$F = 2.82$; $df = 1$ $P = 0.137$	$F = 3.28$; $df = 1$ $P = 0.113$	$F = 1.34$; $df = 1$ $P = 0285$	$F = 0.03$; $df = 1$ $P = 0.875$	$F = 2.60$; $df = 1$ $P = 0.151$	$F = 1.66$; $df = 1$ $P = 0.239$

*$P < 0.05$.
CLZ, Clozapine.

For delay clozapine use at week 8 Δ norclozapine (n = 12).

For early clozapine use at week 18 Δ nor lozapine (n = 8).

When stratified by years since initial pharmacological treatment was started, we found an interesting association between improvement in negative symptom and BMI at both study time points, week 8 and week 18, suggesting the effect of weight increase along the whole follow-up period on those starting clozapine after 3 years of antipsychotic use. Under our personal point of view, one reason might underlie those findings, subjects at initial stages are usually initiated clozapine due to persistent positive symptom, which makes them unable to maintain their daily living activities or present behavioral disorders, whereas later prescription might rely on persistent negative symptom, which might require longer time to detect or at least is treated after other environmental approaches are performed.

Thus, these results also provide novels insights on the temporality of this association. It is well known that clozapine (and olanzapine) may trigger weight gain from the beginning of the antipsychotic treatment, with significant differences during the initial weeks of treatment.[35] In addition, differences in sex applied; in our sample, sex was significantly associated with clinical improvement and BMI in PANSS total score between baseline and week 8, being higher in male than female patients.

Our study has several limitations, such as the small sample size, the low proportion of females, the lack of information regarding physical exercise and dietary intake, and the lack of use of a specific scale for negative symptom, such as Brief Negative Symptom Scale.

Previous results have been described by several authors, not only in clozapine and olanzapine but also in other antipsychotics even with placebo in different studies.[8] An interesting approach relies on the effect of gut-brain hormones,[9] which despite its effect on appetite and food reward,[36] other effects have been described in brain function[37]; indeed, leptin has been described to correlate with negative symptom in schizophrenia.[38]

Our results confirm the association between BMI increase and clinical improvement, specifically in negative symptom suggesting the need of further longitudinal studies involving some of the proposed pathways, such as gut-brain hormones.

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The rest of the authors declare no conflicts of interest.

M.Ga. did the conception and design of the article, acquisition, analyses and interpretation of data, and drafting the manuscript. A.M. did the conception and design of the article, acquisition and interpretation of data, and revising critically for contents. S.B., V.R., S.A., and G.M. did the acquisition and interpretation of data, revising critically for contents. C.O., M.Bi., O.M., M.Go., E.V., M.Be., and E.P. did the revising the manuscript critically for intellectual content and approved the final version of the manuscript. C.G.R. did the conception and design of the article, revising the manuscript critically for intellectual content, and approved the final version of the manuscript.

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5. Discusión y limitaciones

En este trabajo de tesis doctoral se han incluido 3 artículos principales, donde se evalúa la respuesta metabólica, alimentaria y clínica de pacientes con diagnóstico de esquizofrenia refractaria en tratamiento con clozapina. El eje central de estos artículos es conocer mejor cómo funcionan los mecanismos de incremento ponderal de la muestra de estudio con la toma de clozapina para lograr estrategias no farmacológicas que mejorasen el perfil metabólico de estos pacientes. En un primer artículo se describe la capacidad de una intervención psicosocial para mejorar el perfil metabólico y alimentario de los pacientes en estudio. En un segundo artículo, se demuestra el cambio en las preferencias alimentarias, y por último se destaca los beneficios estadísticamente significativos de una intervención educativa liderada por una enfermera especialista en salud mental para la mejora del patrón dietético y de ejercicio fisco de los participantes a estudio. En un último artículo se describe un hallazgo que, aunque contraintuitivo y controvertido (como gran parte de la salud mental) es importante recalcar por su evidencia histórica y poco conocida, de que ciertos pacientes que incrementan su peso con el inicio de la toma de clozapina también mejoran su sintomatología psicótica

La posibilidad de que la psicosis se convierta en una enfermedad crónica es muy alta y, a menudo, aquellos afectados por esta entidad requieren de tratamiento farmacológico, antipsicóticos, a lo largo de sus vidas. Cuando surgió la segunda generación de medicamentos antipsicóticos fue tolerada mejor que la primera, sin embargo, como hemos visto algunos de estos fármacos también tienen efectos adversos y pueden dar lugar a enfermedades físicas. Las investigaciones muestran que la prevalencia de DM tipo 2 y el MetS fue significativamente mayor en pacientes con un trastorno psiquiátrico crónico, particularmente la esquizofrenia. En estos pacientes se estima que un 40% cumple de criterios de Mets y un 50% padece obesidad (Annamalai & Tek, 2015) sin que ningún proveedor de salud haga algo al respecto más allá de un par de analíticas generales al año. Además, no olvidemos que es una población con escaso acceso a los recursos sanitarios, de ahí, que sea una población infradiagnosticada de comorbilidades físicas con un impacto muy negativo sobre su salud que les acorta enormemente su esperanza de vida.

En nuestra práctica clínica, las enfermeras de salud mental vemos como los sujetos con diagnóstico de psicosis refractaria que inician tratamiento psicótropo como es la clozapina, sobre todo, al largo de las primeras semanas, presentan una mejoría clínica. En Nuestro artículo: *"Antipsychotic-Associated Weight Gain and Clinical Improvement Under Clozapine Treatment"*(Garriga et al., 2022) obtuvimos conclusiones asombrosas a la vez que controvertidas. Encontramos que a medida que los pacientes aumentaban de peso,medido como aumento del IMC, con la toma de la clozapina durante las 1eras 8 semanas, se observaba una mejora clínica general a nivel de puntuación total de la PANSS.

Entre las semanas 8 y 18 de seguimiento de los pacientes con clozapina hubo una asociación significativa en las puntuaciones de síntomas negativos de la PANSS, está asociación está condicionada por el sexo, así había mayor mejoría en pacientes de sexo masculino que femenino. También hubo una tendencia significativa en las puntuaciones totales de las PANSS. Encontramos hallazgos parecidos en la literatura, por ejemplo, en una muestra de 74 pacientes, el IMC fue un predictor significativo de psicopatología total evaluada con la Escala Breve de Calificación Psiquiátrica (Meltzer et al., 2003). Estos resultados son importantes también des del punto de vista de la temporalidad. Así pacientes tratados con otros antipsicóticos con más de 3 años de evolución de la enfermedad, que iniciaban clozapina, también aumentaban rápidamente de peso y con ello se presentaba una mejoría clínica (Meltzer et al., 2003).

Así, sabemos que antipsicóticos obesogénicos como son la olanzapina o la clozapina hacen que los pacientes con PEP o con años de evolución de la enfermedad aumenten drásticamente de peso sobre todo entre las semanas 8 y 18 de inicio del tratamiento. ¿Así, salta la pregunta de si el peso es un predictor de mejora clínica en pacientes con esquizofrenia refractaria? Se necesitan más estudios en esta línea de investigación para saber si se trata o no de un hallazgo casual.

¿Desde el punto de vista enfermero, como controlamos ese aumento de peso inicial? ¿Y la aparición incipiente de alteraciones metabólicas?; En la práctica clínica nos encontramos mayoritariamente con una población de años de evolución, a la que nadie les informo de manera clara que la clozapina inducia a una importante ganancia ponderal, con el impacto físico que conlleva, y la vulnerabilidad asociada a padecer alteraciones metabólicas con un elevado impacto cardiovascular. ¿De qué nos sirve como profesionales centrarnos en la mejora clínica para que una persona diagnosticada de psicosis refractaria inicie un tratamiento como es la clozapina, si por otro lado no le explicamos, ni le damos herramientas paracontrolar aquellos efectos secundarios que sabemos que pueden tener un impacto devastador en su salud cardiovascular? Además, y no menos importante, un impacto en su autoestima y calidad de vida. Por lo tanto, los siguientes artículos de esta tesis, van encaminados a encontrar respuestas acerca del aumento

de peso inducido por la clozapina para poder desarrollar estrategias enfermeras de mejora del peso y perfil metabólico.

Este estudio tiene varias limitaciones, como el pequeño tamaño de la muestra, la baja proporción de mujeres, la falta de bibliografía sobre el ejercicio físico y la ingesta dietética, y la falta de uso de una escala específica para síntomas negativos, como la Brief Negative Symptom Scale.

Nuestra siguiente hipótesis para realizar el segundo estudio presentado en esta tesis doctoral: *Food craving and consumption evolution in patients starting treatment with clozapine* (Garriga et al., 2019), fue plantearnos si parte del aumento de peso inducido por la clozapina tenía que ver con cambios en su alimentación. Así, nos planteamos evaluar el deseo por el consumo de diversos alimentos que se encuentran a día de hoy en la dieta española a través de la escala: "*Food Craving Inventory-Spanish version"* (FCI-SP). Y la frecuencia de consumo de estos evaluado con el Cuestionario de Frecuencia de Consumo de Alimentos (CFCA) (Rodríguez et al. 2008), que mide en que frecuencia durante la última semana has consumido toda una serie de alimentos que se agrupan en 16 categorías. Desde el punto de vista enfermero fueron hallazgos muy interesantes, ya que se nos planteaba una ventana de actuación a nivel de educación nutricional. Así, encontramos que los pacientes que partían de mayor IMC cuando iniciaban el tratamiento con clozapina engordaban menos, y seguían con el mismo deseo de consumo de alimentos tipo "fast food" que tenían en el basal y con mayor frecuencia de consumo de estos. En cambio, aquellos que partían de un IMC menos elevado, o con normopeso, la ganancia ponderal durante las 1eras semanas de tratamiento era mayor y estos cambiaban respecto al deseo de consumo de alimentos, hacia carbohidratos y proteínas complejas y también consumían con mayor frecuencia estos alimentos. Estos hallazgos jamás antes se habían probado a través de escalas en pacientes con TMG, a pesar de que no pudimos establecer una relación a nivel longitudinal.

A grandes rasgos, el hecho de que la clozapina haga aumentar de peso a personas con PEP o con años de toma de otros antipsicóticos y que produzca una tendencia general al cambio dietético con preferencia de alimentos muy poco saludables hace patente la necesidad de establecer estrategias para disminuir o mejorar esos resultados. Estos hallazgos son claves para desarrollar estrategias de manejo de peso en pacientes que toman clozapina. Focalizar las intervenciones en educación nutricional, manejo del deseo de consumo de alimentos antojo a través de esta educación dietética, y promoción de la actividad física son claramente una línea de investigación a seguir. Las enfermeras especialistas en salud mental, tenemos un rol protagonista en empoderar a estos pacientes hacia un estilo de vida saludable y así poder llegar a mejorar un hecho tan tan relevante como es la esperanza de vida en esta población.

Este estudio tuvo limitaciones tales como que es posible que los resultados no se puedan generalizar a otros grupos. En primer lugar, nuestros resultados incluyeron una evaluación de seguimiento prospectiva a corto plazo (18 semanas) para predecir futuros antojos de comida y aumento de peso. Se desconocen los efectos a largo plazo del consumo de alimentos antojo, por lo que se necesitan más estudios a largo plazo en esta población. En segundo lugar, la validez de los cuestionarios FCI-SP y el CFCA subjetivos puede verse afectado por el rendimiento cognitivo de nuestra muestra y podrían estar sujetos a sesgos de recuerdo y respuesta. Comparamos los antojos de tipos específicos de alimentos con la ingesta de estas categorías de alimentos. Es posible que algunos antojos de alimentos sean bastante específicos de un alimento individual y no de una clase de alimentos completa. En cuarto lugar, también es posible que los antojos sean un fenómeno condicionado: las personas pueden desear los alimentos que comen con frecuencia.

Finalmente, como principal estudio de esta tesis doctoral, se desarrolló una investigación acera de una intervención en estilo de vida realizado por enfermería: "*Nurse -led lifestyle intervention in a cohort of schizophrenia patients treated with clozapine"* (Mallorquí et al., 2023). Como hemos ido viendo la ganancia ponderal que tienen los pacientes que inician clozapina es importante y el riesgo a padecer obesidad y afecciones metabólicas que en conjunto dan lugar al síndrome metabólico es grande. En los artículos que componen esta tesis describimos varios hallazgos que nos ayudan a predecir el aumento ponderal tan significativo que sufren los pacientes con TMG en tratamiento con clozapina. Por todo ello y como enfermera de salud mental pienso que la educación terapéutica en relación a un estilo de vida saludable es crucial ya que a día de hoy es lo más palpable y potencialmente modificable y que depende en buena medida del paciente.

Motivar y ayudar a la población de estudio que entiendan conceptos básicos nutricionales, a explicarles el impacto de un IMC elevado y/o mejor de un IC elevado en su salud cardio-metabólica asociado a dietas basadas en consumo de alimentos rico en grasas saturadas y azucares, y pobre en fibra y grasas saludables, no es una tarea fácil. Nos encontramos con una población limitada por la propia enfermedad en muchas áreas: cognitiva, social, y funcional. Con frecuente precariedad económica y escaso apoyo social. Lo cual hace que desarrollar la intervención fuese todo un reto para la investigadora principal y sus hallazgos una luz de esperanza.

Se realizo una intervención educativa basada en hábitos dietéticos saludables y promoción del ejercicio físico de 8 semanas de duración liderado por una enfermera. Los resultados mostraron que las intervenciones en el estilo de vida son más seguras y efectivas para promover la disminución o el

mantenimiento del peso y demás parámetros metabólicos de riesgo cardiovascular y se pueden administrar a bajo coste, son seguras y mejoran la calidad de vida. Después de nuestra intervención los parámetros antropométricos como el peso, IMC y perímetro abdominal claramente mejoraron al finalizar la intervención, aunque algunos de ellos no se mantuvieron a los tres meses de acabar.

El perímetro abdominal se considera un predictor muy valioso del síndrome metabólico y a día de hoy, se considera que es el mejor sustituto antropométrico para predecir la resistencia a la insulina asociada al consumo de clozapina en usuarios no diabéticos (Barton et al., 2020). El Índice Cintura-Cadera (ICC) también mejoro a los tres meses de haber iniciado la intervención. Entonces podría ser esencial para no solo pensar que es efectivo en 1eros episodios sino también en pacientes de años de evolución a los que a veces se da por perdidos, como fue el caso de esta investigación. El ICC es un indicador antropométrico preciso para predecir la hipertensión arterial y el riesgo cardiovascular y hoy en día se considera uno de los mejores predictores del riesgo cardiovascular más allá del IMC (Czernichow et al., 2011). Por tanto, su mejoría a los tres meses de finalizar las sesiones de estilo de vida demuestra la eficacia de la intervenciónen la reducción de uno de los principales predictores de riesgo cardiovascular.

El programa australiano *Keep Body in Mind* describió hallazgos similares con pacientes diagnosticados con un primer episodio de psicosis, estos redujeron su peso inicial en más del 7 % pero no permanecieron más allá de los tres meses posteriores a la intervención (Watkins et al., 2019).

En particular, los niveles de colesterol HDL mejoraron significativamente al final de la intervención y mantuvieron un nivel de mejora significativa 3 meses después de la intervención. El nivel de colesterol total solo mejoró significativamente a las 8 semanas. Pero pensemos que los mejores niveles de colesterol HDL ayudan a reducir progresivamente los niveles de LDL y colesterol total. Por todo ello, junto con los resultados del cuestionario DIETMED, escala que evalúa un estilo de dieta mediterránea, en los que se mostró una mejora de la adherencia a la dieta mediterránea a los tres meses de la intervención. Esto nos hace pensar que los pacientes realmente cambiaron sus hábitos dietéticos durante la intervención y hubo una tendencia a mantenerlos al menos durante los siguientes tres meses.

También hubo una mejora en la actividad física descrita por el cuestionario Internacional de Actividad Física: IPAQ, aunque esta no se mantuvo a los tres meses. Observamos que partíamos de una muestra adicta a alimentos basura, con una escasa actividad física y un elevado consumo de tabaco, muestras similares se describen en la literatura cuando hablamos de población con TMG. Es especialmente importante en esta población en tratamiento con clozapina, medir la presión arterial, la glucosa, triglicéridos y colesterol en ayunas al igual que las mediciones de CC, IMC y ICC, aun mas en pacientes obesos, con dislipemia y en estado pre-diabético o diabético. El riesgo cardiovascular de estas personas solo se puede saber monitoreando el estado cardiometabólico de cada paciente individualmente. Hasta la fecha, no se han encontrado estudios de esta índole, tan completos, en los que se hayan evaluado el pre- post de tantas variables antropométricas y metabólicas además de los cuestionaros de consumo de alimentos y de ejercicio físico.

Por esta razón los hallazgos son relevantes y esperamos que susciten realizar más estudios longitudinales para poder abrir nuevos caminos de tratamiento. Por tanto y como hemos visto, después de nuestra intervención hubo mejorar significativa de diversos parámetros tanto antropométricos como metabólicos, y la mejora de algunos de ellos son predictores de laprevención o mejora de enfermedad metabólica como es la hipertensión, HTA o la DMT2. Además, estos se mantuvieron mientras duraba la intervención o/y de manera posterior, lo que nos hace pensar que tenemos ahí un potencial tratamiento no invasivo para la mejora de la salud cardiovascular. Las personas con TMG tienen muchos factores en contra para mantener un peso y unos parámetros metabólicos adecuados debido a una posible vulnerabilidad epigenética que favorece el desarrollo de la enfermedad mental y los trastornos metabólicos debido a haber sufrido complicaciones intrautero/obstétricas y a algunos psicofármacos, como la clozapina, que han de tomar toda la vida. Sin embargo, hay estrategias educativas que pueden prevenir el riesgo de la obesidad y el riesgo cardiovascular.

Entre las limitaciones más importantes de este estudio se encuentra el tamaño de la muestra. Fue difícil aumentar el número de casos por las propias características de la enfermedad y del tratamiento y por el número de visitas médicas que requieren. Todo ello dificulta que estos pacientes acepten participar en un proyecto que requiere compromiso durante varias semanas. Otra limitación fue el diseño del estudio que no incorporó un grupo control con las mismas características clínicas y sociodemográficas de los participantes. Ello se debió a que este estudio es interdisciplinar y tenía como principal objetivo evaluar la efectividad de un medicamento.

6. Investigaciones futuras e implicaciones clínicas.

Se necesitan ECA prospectivos a futuro para investigar los beneficios de la mejora de la dieta y la práctica del ejercicio en los diferentes ámbitos de salud de las personas con trastornos mentales tales como la esquizofrenia.

Una línea de investigación actual y futura es poder establecer qué tipo de pacientes se beneficiarían más de su participación en grupos de mejora de estilo de vida debido a su reserva cognitiva, insight...etc para una mayor efectividad y mayor efecto de los beneficios a medio –largo plazo.

Los resultados deben considerarse con cautela dada la falta de potencia de la investigación

7. Implicaciones para la práctica

Para las personas con esquizofrenia, el aumento de peso es un problema común. La pérdida de este se puede lograr con intervenciones no farmacológicas (que promuevan la actividad física y cambios en la dieta). Sin embargo, no podemos asegurar un tipo de intervención más efectiva que otra porque está limitada por el pequeño número de estudios y la variabilidad metodológica de estos con intervenciones de diversa índole, así como la duración

El estudio está limitado principalmente por su tamaño y por la falta de controles relacionados con las características de edad, sexo y características socio demográficas. Esto se debió a la naturaleza de este estudio, que pretendía evaluar la eficacia de una intervención de estilo de vida en el mundo real, y que se ofreció a todos los sujetos que cumplían con los criterios de inclusión de modo que no se pudo llevar a cabo la aleatorización y la posterior comparación. Algunas de las relaciones transversales marginales identificadas son resultados probables de esta limitación y siguen siendo difíciles de interpretar como resultado. La capacidad de cuantificar y medir con precisión todos los riesgos tradicionales asociados a la EM, como los antecedentes familiares de diabetes, el origen étnico, la dieta y los niveles de ejercicio, el consumo de tóxicos es limitada. A estos pacientes debido a la propia enfermedad les cuesta conseguir una motivación para cambiar y mantener hábitos saludables, así mismo comprometerse a participar en un programa de intervención a medio-largo plazo.

8. Conclusión

Nuestros resultados confirman la asociación entre el aumento del IMC y la mejoría clínica, específicamente en los síntomas negativos de la enfermedad. Es decir, no se sabe aún porque mecanismos aquellas personas que aumentan de peso, mejoran clínicamente. Una de las posibles explicaciones serían las neurohormonas, que son las que actúan en las vías intestino–cerebro, lo que sugiere la necesidad de más estudios longitudinales que involucren estos factores. A pesar de estos resultados, no podemos dejar que los pacientes aumenten de peso indiscriminadamente sin actuar al respecto, con las consecuencias que esto conlleva a nivel cardiometabolico. Ya que este resultado ha sido un hallazgo puntual y no existe una certeza clara de que mecanismo subyacen para obtener estos resultados.

La clozapina es un fármaco que ayuda a la estabilidad clínica de los pacientes y a aumentar la esperanza de vida de estos, pero su impacto metabólico en la salud física aumenta el riesgo cardiovascular. El aumento de peso que la mayoría de los pacientes sufren, y demás alteraciones metabólicas, en gran parte son debidos al cambio de patrón dietético y de consumo de alimentos, más ricos en grasas saturadas.

Los pacientes que partían de bajo peso al inicio del tratamiento con clozapina y hasta las 18 semanas de seguimiento cambiaban su patrón alimentario por alimentos más ricos en grasas y había también un mayor consumo de este tipo de alimentos, mientras que los que partían de un normopeso o sobrepeso también cambiaron su patrón dietético y se mantenía y/o aumentaba el consumo de alimentos tipos “fast food”, pero no se puedo correlacionar de manera significativa con el IMC. Estos resultados nos brindan una clara línea de actuación a las enfermeras de salud mental respecto a educar para mejorar el estilo de vida (alimentación y ejercicio físico) de los pacientes con TMG que toman clozapina.

Las enfermeras de práctica avanzada especialistas en salud mental deben contemplar la salud física como un aspecto crucial a trabajar en una persona con una patología mental como es la esquizofrenia. Se da por supuesto que el aumento de peso es un efecto secundario del tratamiento y que, por la propia índole de la enfermedad, no pueden mejorar su estilo de vida... Los resultados de nuestro estudio: *Nurse-led lifestyle intervention in a cohort of schizophrenia patients treated with clozapine*, confirman los hallazgos de estudios previos en los que las intervenciones no farmacológicas pueden reducir significativamente el peso y el riesgo cardiometabólico asociado y mejorar el estilo de vida en una cohorte de pacientes en tratamiento con clozapina. Nuestros resultados muestran no sólo una mejoría a corto plazo sino también a

medio plazo (3 meses de post intervención) por tanto sí que se pueden logran cambios a nivel antropométrico y metabólico y de estilo de vida en personas con TMG en tratamiento con clozapina.

Se deben medir los parámetros de riesgo cardiovascular tanto antropométricos, de estilo de vida, como analíticos y en especial, y tal como hemos visto, las medidas de la circunferencia abdominal y el índice cintura-cadera. Estos se deben medir de manera sistemática, una idea, y futuro proyecto de investigación sería el desarrollo de un check list de parámetros antropométricos, metabólicos y de estilo de vida, para esta población realizando un correcto registro y evaluación. A la par que realizar grupos educativos centrados en alimentación saludable y promoción del ejercicio físico para poder empoderar a las personas con esquizofrenia en materia de salud cardiovascular.

Es importante realizar más estudios tipo ECA longitudinales para corroborar la eficacia de estos grupos más a largo plazo ya que actualmente en la literatura disponemos de pocos ECA que analicen tratamientos NO farmacológicos para el manejo de la obesidad y síndrome metabólico en pacientes tratados con clozapina.

Los estudios realizados para intervenciones farmacológicas sugieren que fármacos como la metformina, el topiramato y aripiprazol pueden ser eficaces, pero con un impacto clínico limitado. Una línea de investigación interesante es poder hacer un cribaje para aquellos enfermos de años de evolución de la enfermedad a nivel neuropsicológico para poder ver quienes presentan las funciones ejecutivas más preservadas y por tanto probablemente beneficiarse más de este tipo de intervenciones educativas, etc.

La modificación del estilo de vida se considera un tratamiento de primera línea para las anomalías metabólicas y se ha encontrado que es eficaz para detener la progresión del síndrome metabólico. La modificación del estilo de vida implica evaluar la dieta y el estado nutricional y el régimen de ejercicio de la persona, y realizar cambios para influir en la reducción de peso y aumentar la actividad física.

Nuestros resultados son alentadores en relación a que el cambio de estilo de vida es posible en esta población, aunque con limitaciones, es una vía de estudio para mejorar el impacto cardiovascular devastador en pacientes con TMG con uso de clozapina.

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9. Referencias bibliográficas

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10. Anexos

UNIVERSITAT JAUME I
Escola de Doctorat · ED

(Nombre)..... Clemente Garcia Rizo ....., como coautor/ coautora doy mi autorización a (Nombre del doctorando/doctoranda) Andrea Mallorqui Molina..para la presentación de las siguientes publicaciones como parte de su tesis doctoral.

Relación de publicaciones:

Como autor senior de las publicaciones siguientes así como co director del proyecto de tesis doctoral de la doctoranda Andrea Mallorqui Molina, confirmo que las siguientes publicaciones no se han utilizado previamente ni se utilizaran en ningun otro proyecto de tesis doctoral.

Nurse-led lifestyle intervention in a cohort of schizophrenia patients treated with clozapine.
Mallorquí A, Oliveira C, Ríos J, Isla-Pera MP, Gil-Badenes J, Amoretti S, Bernardo M, Vieta E, Parellada E, Garriga M, García-Rizo C.
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Asimismo, renuncio a poder utilizar estas publicaciones como parte de otra tesis doctoral.

Y para que conste firmo el presente documento,

Conocedor de la normativa vigente, como profesor de la Universidad de Barcelona, suscribo este documento en mi nombre y el resto de autores.

Lugar, fecha y firma

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Todo ello, atendiendo al artículo 28 del Reglamento de los estudios de doctorado de la Universitat Jaume I de Castelló, regulados por el RD 99/2011, en la Universitat Jaume I (Aprobado en la sesión nº 8/2020 del Consejo de Gobierno de 02 /10/2020):

"(...)

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