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UNIVERSIDAD CATÓLICA DE MURCIA

ESCUELA INTERNACIONAL DE DOCTORADO

Programa de Doctorado en Ciencias de la Salud

Patrones de prescripción médica relacionados con el uso de benzodiazepinas en Salud Mental en la Región de Murcia (2016-2017).

Autor:

Jorge Simal Aguado

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AUTORIZACIÓN DEL DIRECTOR DE LA TESIS PARA SU PRESENTACIÓN

El Dr. D. Alejandro Galindo Tovar y el Dr. D. Juan Antonio García Carmona como Directores[1] de la Tesis Doctoral titulada "Patrones de prescripción médica relacionados con el uso de benzodiazepinas en Salud Mental en la Región de Murcia(2016-2017)" realizada por D. Jorge Simal Aguado en el Programa de Doctorado Ciencias de la Salud, autoriza su presentación a trámite dado que reúne las condiciones necesarias para su defensa.

Lo que firmo, para dar cumplimiento al Real Decreto 99/2011 de 28 de enero, en Murcia a 21 de Julio de 2022.

Alejandro Galindo Tovar

Juan Antonio García Carmona

[1] Si la Tesis está dirigida por más de un Director tienen que constar y firmar ambos.

RESUMEN

Las enfermedades mentales engloban un gran número de dolencias, desde patologías comunes, como trastornos del ánimo, otras causadas por el abuso de sustancias y enfermedades mentales graves, como esquizofrenia y trastorno bipolar. Dado que los trastornos mentales producen consecuencias importantes a nivel psicosocial, económico y de salud pública, la Organización Mundial de la Salud (OMS) atribuye un carácter prioritario su estudio y tratamiento precoz.

Para el tratamiento farmacológico de las enfermedades mentales se utilizan diferentes fármacos, como antipsicóticos, antidepresivos, estabilizadores del ánimo y benzodiazepinas. A pesar de que las benzodiazepinas son un grupo de fármacos muy utilizados, los efectos secundarios que pueden producir sobre el estado de ánimo, a nivel cognitivos y el potencial desarrollo de dependencia, provocan un continuo debate médico sobre su adecuada prescripción, tanto a nivel de atención primaria como en Salud Mental. La introducción en la práctica clínica de los nuevos fármacos antipsicóticos inyectables de larga duración (LAIs) ha supuesto una mejora en el tratamiento de mantenimiento de los pacientes en Salud Mental, sin embargo, se desconoce el impacto sobre el uso de otros psicofármacos en estos pacientes y el coste económico asociado. Entre los LAIs más utilizados en España se encuentran, risperidona, su metabolito activo o palmitato de paliperidona y aripiprazol. Tanto a nivel nacional como en la Región de Murcia, su impacto en los tratamientos de Salud Mental ha sido poco estudiado.

Por tanto, nuestro objetivo fue estudiar los patrones de prescripción de benzodiazepinas en pacientes de Salud Mental de la Región de Murcia y analizar las posibles diferencias de uso de estos fármacos así como el impacto de otros psicofármacos, en particular los LAIs.

Nuestros resultados mostraron que ser mujer (OR=1.56, 95%CI=1,05–2.29, p=0.024), ser usuario de drogas de abuso (OR=1.67, 95%CI=1.12 -2.47, p=0.011) y sufrir un trastorno mental afectivo (OR=1.54, 95%CI=1.35–1.82, p=0.040) incrementan el riesgo de consumir benzodiazepinas. En cambio, el uso de LAIs reducen significativamente el riesgo de tomar benzodiazepinas en comparación con la toma de antipsicóticos orales (OR=5.226, 95%CI=3.18–8.57, p=0.001). El 14% de los pacientes con alguna enfermedad mental grave, que utilizaban LAIs, eran tratados en monoterapia. El principal tipo de medicación concomitante fueron las benzodiazepinas con una media de 18.22±1.57 mg/día, de equivalentes de diazepam. Entre los LAIs, las formulaciones inyectables de paliperidona mensual y trimestral se asociaron a un menor consumo de benzodiazepinas (12.56±2.16 y 7.87±2.82, p=0.0001, respectivamente), en comparación con antipsicóticos inyectables bisemanales y aripiprazol mensual (37.19±4.65 y 26.05±2.37, respectivamente).

Resultados similares se obtuvieron en los grupos de pacientes diagnosticados de esquizofrenia o trastorno de personalidad. Entre los 277 pacientes con esquizofrenia, ser tratado con antipsicóticos orales incrementa el riesgo de tomar benzodiazepinas (p=0.001; RR=3.30; 95%CI=1.7–6.4). Por su parte, entre los LAIs, los bisemanales se asociaron un mayor riesgo de uso concomitante de benzodiazepinas (p=0.036). Entre los 116 pacientes con Trastorno de personalidad, no encontramos diferencias estadísticamente significativas entre pacientes tratados LAIs y con antipsicóticos orales (p=0.096) sobre el riesgo de ser prescrito con benzodiazepinas. Sin embargo, sí demostramos diferencias estadísticamente significativas en cuanto al número de benzodiazepinas utilizadas entre los diferentes LAIs (p=0.001), en concreto con LAIs de paliperidona mensual y trimestral, en comparación aripiprazol (p=0.045, p=0.001, respectivamente) y entre LAIs de paliperidona trimestral y risperidona (p=0.025).

En conclusión, el uso de benzodiazepinas en pacientes de Salud Mental es elevado, siendo la mayoría de los pacientes tratados con, al menos, una benzodiazepina, con una dosis diaria de 25 mg equivalentes de diazepam. Además, el uso de LAIs reduce la necesidad de utilización de benzodiazepinas concomitantes, especialmente las formulaciones inyectables de larga duración de paliperidona.

Palabras clave: Benzodiazepinas; Salud Mental; dosis equivalentes de diazepam; antipsicóticos inyectables de larga duración.

ABSTRACT

Mental disorders include a wide range of conditions such as mood disorders, substance use disorders and severe mental disorders such as schizophrenia and bipolar disorder. The World Health Organization (WHO) encourages the study and early treatment of mental disorders due to their major psychosocial, economic and public health consequences.

Antipsychotics, antidepressants, mood stabilisers and benzodiazepines are used for the pharmacological treatment of mental disorders. Although benzodiazepines are a widely used group of drugs, they can produce side effects on mood and cognitive level and also increase the risk of dependence. For that reason, it is important their appropriate prescription at both, primary and Mental Health care. The availability of the new long-acting injectable antipsychotics drugs (LAIs) in clinical practice has led to an improvement in the maintenance treatment of mental health disorders; however, their impact on the use of other psychotropic drugs is unknown. Paliperidone palmitate-LAIs, aripiprazole-LAI and risperidone-LAI are the most used LAIs in Spain. Nonetheless, their impact on Mental Health treatments has been little studied in Spain and, in particular, in the Region of Murcia.

Therefore, the aim of our study was to evaluate the prescription patterns of benzodiazepines and to analyse the impact of the LAIs in a cohort of patients from Mental Health in the Region of Murcia.

Our results showed that being female (OR=1.56, 95%CI=1.05-2.29, p=0.024), drug user (OR=1.67, 95%CI=1.12-2.47, p=0.011) and to suffer an affective disorder (OR=1.54 95%CI=1.35-1.82, p=0.040) increased the risk of benzodiazepine use. In contrast, being treated with LAIs, instead oral antipsychotics, significantly reduced the risk of being prescribed with benzodiazepines (OR=5.226, 95%CI=3.18-8.57, p=0.001). Nonetheless, among the patients diagnosed with a severe mental disorder and treated with LAIs, only the 14% of were treated in monotherapy. The main concomitant medication was benzodiazepines with a mean of 18.22±1.57 mg/day of diazepam equivalents. 1-month and 3-month LAIs of paliperidone were associated with lower diazepam equivalents intake (12.56±2.16 and 7.87±2.82, p=0.0001, respectively), compared to biweekly and aripiprazole LAIs (37.19±4.65 and 26.05±2.37, respectively).

We obtained similar results in the groups of patients diagnosed with schizophrenia and personality disorder. Among the 277 patients with schizophrenia, the risk of being prescribed with benzodiazepines were increased when they were treated with oral antipsychotics (p=0.001; RR=3.30; 95%CI=1.7-6.4) compared with LAIs. Among LAIs, biweekly formulations were associated with an increased risk of

use concomitant benzodiazepines (p=0.036). In contrast, we found no differences between patients treated with LAIs and oral antipsychotics (p=0.096) in the 116 patients diagnosed with personality disorder. However, we found significant differences in the number of benzodiazepines used between the different LAIs (p=0.001), specifically with 1-month and 3-month paliperidone-LAIs compared to aripiprazole (p=0.045, p=0.001, respectively) and between 3-month paliperidone-LAI compared with risperidone-LAI (p=0.025).

In conclusion, the use of benzodiazepines in mental health is common. Most patients were treated with at least one benzodiazepine with a daily dose of 25 mg diazepam equivalents. Moreover, the use of LAIs reduces the need of concomitant benzodiazepines.

Keywords: Benzodiazepines; Mental health; diazepam equivalents; long-acting injectable antipsychotics.

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TESIS POR COMPENDIO DE PUBLICACIONES

La Tesis Doctoral, titulada "Patrones de prescripción médica relacionados con el uso de benzodiazepinas en Salud Mental en la Región de Murcia (2016-2017) fue realizada como compendio de cuatro trabajos publicados.

Long-acting injectable antipsychotics: analysis of prescription patterns and patient characteristics in mental health from a spanish real-world study. García-Carmona JA, Simal-Aguado J, Campos-Navarro MP, Valdivia-Muñoz F, Galindo-Tovar A. Clin Drug Investig 2020; 40(5):459-468. doi: 10.1007/s40261-020-00913-7. IF: 2.86

Evaluation of long-acting injectable antipsychotics with the corresponding oral formulation in a cohort of patients with schizophrenia: a real-world study in Spain. García-Carmona JA, Simal-Aguado J, Campos-Navarro MP, Valdivia-Muñoz F, Galindo-Tovar A. Int Clin Psychopharmacol. 2021; 36(1):18-24. doi: 10.1097/YIC.0000000000000339. IF: 1.66

Evaluation of Risk Factors Associated to Prescription of Benzodiazepines and its Patterns in a Cohort of Patients from Mental Health: A Real World Study in Spain. Simal-Aguado J, Campos-Navarro MP, Valdivia-Muñoz F, Galindo-Tovar A, García-Carmona JA. Psychopharmacol Bull 2021; 51(1):81-93. IF: 1.09

Off-label use of second-generation antipsychotics in borderline personality disorder: a comparative real-world study among oral and long-acting injectables in Spain. García- Carmona JA, Simal-Aguado J, Campos-Navarro MP, Valdivia-Muñoz F, Galindo-Tovar A. Int Clin Psychopharmacol. 2021; 36(4):201-207. doi: 10.1097/YIC.0000000000000357. IF: 1.66

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SIGLAS Y ABREVIATURAS

ADT	Antidepresivos tricíclicos
AEMPS	Agencia Española de Medicamentos y Productos Sanitarios
ARNm	Ácido ribonucleico mensajero
D	Dopaminérgico
DDD	Dosis diaria definida
DED10	Dosis equivalente a 10 mg de diazepam
DUTmáx	Dosis terapéutica máxima
EEUU	Estados Unidos
FDA	Food and Drug Administration
GABA	Ácido gamma-aminobutírico
5-HT	5-hidroxitriptamina
IRDN	Inhibidores de la recaptación de dopamina y noradrenalina
IRNA	Inhibidores de la recaptación de noradrenalina
IRSN	Inhibidores selectivos de la recaptación de serotonina y noradrenalina
ISRS	Inhibidores selectivos de la recaptación de serotonina
LAI	Antipsicótico inyectable de larga duración
MT	Melatonina
NaSSA	Antidepresivos noradrenérgicos o serotoninérgicos selectivos
OMS	Organización Mundial de la Salud
PP1M	Palmitato de paliperidona mensual
PP3M	Palmitato de paliperidona trimestral
SNC	Sistema nervioso central

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I- INTRODUCCIÓN

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1.1 BENZODIAZEPINAS

A lo largo de la historia se han descubierto y administrado diferentes sustancias con efectos sedantes, como el opio, que fue utilizado por diferentes culturas. En la primera mitad del siglo XX, aparecieron los barbitúricos. El abuso de estos fármacos producía adicción con mucha frecuencia y una gran cantidad de muertes por intoxicación. En el año 1949 se descubrió la primera benzodiazepina, el clordiazepóxido, una sustancia con propiedades sedantes, miorrelajantes y anticonvulsivantes (1). Con el desarrollo e investigación de las benzodiazepinas, los barbitúricos fueron relegados a un segundo lugar. Las benzodiazepinas eran más seguras, mejor toleradas, con menores efectos adversos y con una gran eficacia clínica. Debido al gran interés clínico suscitado por este grupo de fármacos, se desarrollaron una gran cantidad de sustancias benzodiazepínicas, aunque para uso clínico, hoy en día, haya poco más de una treintena de ellas autorizadas (2).

Más tarde, en los años ochenta, se desarrolló otro grupo de fármacos derivados de las benzodiazepinas, los conocidos como fármacos "Z", utilizados principalmente como hipnóticos. Este grupo de fármacos tiene muchos menos efectos adversos que las benzodiazepinas, pero su uso se limita a tratar trastornos del sueño.

Todas las guías clínicas exponen que el tratamiento con benzodiazepinas debe ser médicamente supervisado y a corto plazo, evitando así gran parte de los efectos adversos que pudieran producirse. Sin embargo, es frecuente el abuso y la dependencia de estos fármacos que son utilizados, por muchos pacientes, durante años (3).

Las benzodiazepinas son fármacos con una estructura química compuesta por un anillo benzeno fusionado con un anillo de diazepina de siete miembros (Figura 1). El anillo de diazepina contiene dos átomos de nitrógeno, normalmente en las posiciones 1,4-diazepina, y un anillo de benceno con un grupo fenilo unido en la posición 5. Existen excepciones como el clobazam que presenta los átomos de nitrógeno en las posiciones 1 y 5 (Tabla 1). Las diferentes modificaciones en las cuatro posiciones restantes dan lugar a las diferentes benzodiazepinas. Son los fármacos más utilizados por su acción ansiolítica e hipnótica. Su utilización se encuentra muy extendida ya que son medicamentos seguros y eficaces (4).

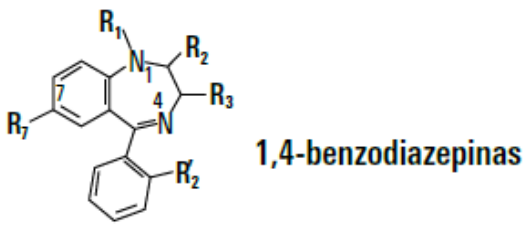

Figura 1. Estructura básica de las 1,4 benzodiazepinas.

Tabla 1. Sustituyentes de algunas 1,4-benzodiazepinas simples (5).

	R_1	R_2	R_3	R_7	R'_2
Lorazepam	-H	=O	-OH	-Cl	-Cl
Quazepam	$-CF_3$	=S	-H	-Cl	-F
Pinazepam	$-CH_2-C\equiv CH$	=O	-H	-Cl	-H
Lormetazepam	$-CH_3$	=O	-OH	-Cl	-Cl
Diazepam	$-CH_3$	=O	-H	-Cl	-H
Clonazepam	-H	=O	-H	$-NO_2$	-Cl

1.1.1 Mecanismo de acción

Las benzodiazepinas actúan sobre los receptores del ácido gamma-aminobutírico (GABA). Todos los fármacos de la familia de las benzodiazepinas se fijan al receptor ionotrópico $GABA_A$ en un sitio de unión diferente al del GABA, que actúa como modulador alostérico, incrementando la afinidad del GABA por el receptor facilitando la apertura del canal de cloruro. Aumentan la frecuencia de apertura del canal inducida por GABA sin producir cambios en la conductancia o el tiempo medio de apertura. Por tanto, potencian así la respuesta inhibitoria sobre el sistema nervioso central (SNC) (5, 3).

Las propiedades farmacológicas de cada subtipo de receptor $GABA_A$ vienen determinadas por las diferentes combinaciones de sus subunidades (6, 7). El número y el tipo de subunidad varían dependiendo de la localización del receptor dentro del SNC (8) (Figura 2). Un total de 19 poliéptidos (α1-6, β1-3, γ1-3, δ, ε, π, θ y ρ1-3) se ensamblan mediante diferentes combinaciones dando lugar a las diferentes subunidades del receptor $GABA_A$ (9). Por ejemplo, los receptores α-1-$GABA_A$ se encargan de regular la sedación, la amnesia y la acción anticonvulsivante mientras que la acción ansiolítica está regulada por los receptores α-2-$GABA_A$ (10, 11).

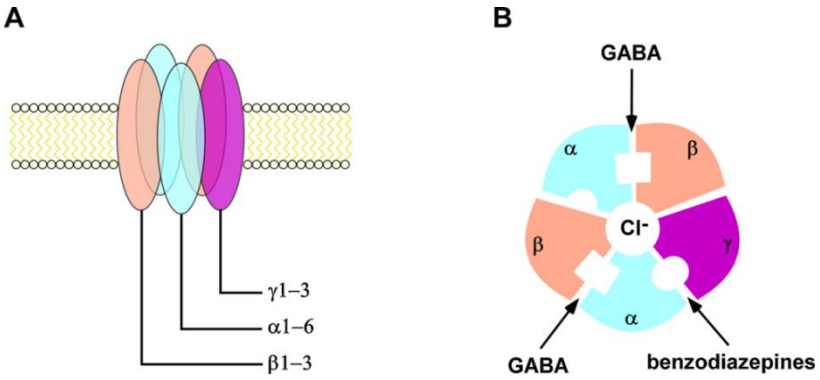

Figura 2. (12) Estructura de los receptores $GABA_A$. (A) La mayoría de los receptores $GABA_A$ están compuestos por cinco subunidades divididas en α, β y subfamilias γ. (B) Vista tranversal del receptor $GABA_A$. Las cinco subunidades se juntan formando el canal permeable de cloro. Los lugares de unión del GABA están localizados en el espacio entre las subunidades α y β, mientras que los lugares de unión de las benzodiazepinas se localizan en el espacio entre las subunidades α y γ.

1.1.2 Potencia y farmacocinética

Se debe elegir, para cada situación y paciente en particular, la benzodiazepina adecuada, considerando su perfil farmacocinético. Los factores farmacocinéticos a considerar son: la vía de administración, la velocidad y el grado de absorción, el metabolismo, la formación de metabolitos activos, la vía de eliminación y la interacción con otros fármacos y sustancias (13).

La vía de administración preferente es la vía oral, ya que la mayoría de las benzodiazepinas se absorben rápidamente y presentan una biodisponibilidad entre el 80% y el 100%. Una excepción es el midazolam, utilizado vía intravenosa, ya que presenta una biodisponibilidad por vía oral del 44% (14). Esto es debido a que su metabolismo se produce a través del enzima 3A5 del citocromo P-450 en el intestino, donde se reduce un 50% la dosis que llega al torrente sanguíneo (15). La concentración plasmática máxima se alcanza, dependiendo de la benzodiazepina, entre minutos y horas tras la administración. La administración intramuscular no se suele utilizar debido a su baja absorción, por ejemplo, lorazepam y midazolam se absorben relativamente rápido pero diazepam y clorazepato se absorben más lentamente (16). Por su parte, la administración intranasal alcanza los niveles de concentración plasmática máxima antes que la vía oral (17).

La liposolubilidad determina la velocidad de difusión de cada fármaco. Es característico de las benzodiazepinas que el paso a través de la barrera hematoencefálica se produce rápidamente (18). Naturalmente, cuanto mayor sea la velocidad de difusión, antes se producirán los efectos farmacodinámicos. Las

benzodiazepinas también atraviesan la barrera placentaria. Por este motivo, el uso de benzodiazepinas durante el embarazo está contraindicado, salvo casos puntuales en los que el facultativo decida que el beneficio es mayor que el riesgo (19, 20).

La mayoría de las benzodiazepinas se metabolizan a través de reacciones de oxidación en el hígado. El citrocromo P450 facilita estas reacciones. Algunas benzodiazepinas como, por ejemplo, lorazepam y oxazepam, requieren únicamente reacciones de glucurono-conjugación, a nivel hepático, para ser eliminadas (21).

Los metabolitos activos aparecen tras el primer paso hepático, en la mayoría de las benzodiazepinas. Debido a la presencia de los metabolitos activos, los efectos de las benzodiazepinas se prolongan (21). En los pacientes con daño hepático es de suma importancia seleccionar benzodiazepinas que no utilicen esta vía metabólica, eligiendo aquellas que utilicen reacciones de conjugación (5).

Las benzodiazepinas pueden clasificarse según su tiempo de acción, semivida de eliminación y la estructura química (Tabla 2). Respecto a su tiempo de acción, Manchester y cols., (14) clasifican como de acción corta a aquellas con una duración menor a 24 horas y de acción larga aquellas cuyos efectos duran más de 24 horas. Por otra parte, según su semivida de eliminación, las benzodiazepinas pueden ser clasificadas como: a) de larga duración, aquellas con una semivida de eliminación mayor a 40 horas; b) de duración intermedia, entre 12 y 40 horas; y c) de duración corta, aquellas con una semivida de eliminación de entre 1 y 12 horas (23). Otra clasificación muy utilizada en función de la semivida de eliminación es: a) de larga duración, como aquellas con una semivida igual o mayor a 24 horas; b) de duración intermedia y corta, semivida entre 5 y 24 horas; y c) las de semivida ultracorta, inferior a 5 horas (14, 24).

Tabla 2. Clasificación de las principales benzodiazepinas según su vida media y características farmacocinéticas (22).

Fármaco	Semivida plasmática (horas)	Semivida eliminación (horas)	Metabolitos activos	Absorción	Uso	Dosis (mg/día)	Ruta Metabólica
Benzodiazepinas Vida Media Corta							
Midazolam	1-3	3-4,2	SÍ	Muy rápida	Hipnótico/ Sedante	7,5-15	Oxidación
Triazolam	2-4	1,5-5	NO	Muy rápida	Hipnótico/ Sedante	0,125-0,25	Oxidación
Bentazepam	3-4,5	2,2-4,5	NO	Rápida	Ansiolítico	50-150	Oxidación
Brotizolam	5	4-8	SÍ	Rápida	Hipnótico/ Sedante	0,25	Oxidación
Clotiazepam	5-6	4,6-10	NO	Muy rápida	Ansiolítico	5-60	Oxidación
Loprazolam	7-8	4-15	SÍ	Rápida	Hipnótico/ Sedante	1-2	Conjugación
Lormetazepam	10	10-11	SÍ	Muy rápida	Hipnótico/ Sedante	0,5-2	Conjugación
Lorazepam	12	10-20	NO	Lenta	Ansiolítico	1,5-10	Conjugación
Alprazolam	11-13	12-15	NO	Muy rápida	Ansiolítico	0,5-4	Oxidación
Temazepam	8-20	8-22	NO	Rápida	Hipnótico/ Sedante	10-20	Conjugación
Benzodiazepinas Vida Media Larga							
Pinazepam	15-17	33-66	SÍ	Muy rápida	Ansiolítico	5-20	Oxidación
Bromazepam	8-19	8-32	SÍ	Muy rápida	Ansiolítico	3,6-4,5	Oxidación
Clobazam	20	10-50	SÍ	Lenta	Ansiolítico	20-80	Oxidación
Clordiazepóxido	7-28	24-48	SÍ	Lenta	Ansiolítico	15-100	Oxidación
Diazepam	15-60	30-100	SÍ	Muy rápida	Ansiolítico	6-40	Oxidación
Quazepam	25-41	39	SÍ	Muy rápida	Hipnótico/ Sedante	15	Oxidación
Clorazepato	40-60	30-100	SÍ	Rápida	Ansiolítico	30-60	Oxidación
Medazepam	26-53	36-96	SÍ	Muy rápida	Ansiolítico	10-30	Oxidación
Ketazolam	50-100	50-100	SÍ	Lenta	Ansiolítico	15-60	Oxidación
Flurazepam	51-100	47-100	SÍ	Muy rápida	Hipnótico/ Sedante	15-30	Oxidación

En definitiva, cada benzodiazepina posee un perfil farmacocinético diferente, lo que dificulta la comparación entre ellas. Sin embargo, esta variabilidad permite a los facultativos tener un amplio abanico de elección fármaco-terapéutico para cada

paciente y cada situación; pudiendo elegir benzodiazepinas más o menos potentes o con una dosis diaria mayor o menor (tabla 3).

Tabla 3. DED10: Dosis equivalente a 10mg de Diazepam, DDD: Dosis diaria definida, DTUmáx: Dosis terapéutica máxima. Potencia. De 24 Benzodiazepinas (25).

Benzodiazepina	DED10	DDD	DTUmáx	Potencia
Alprazolam	0,5	1	4	Alta
Bromazepam	6	10	18	Alta
Brotizolam	0,25-0,5	0,35	0,25	Alta
Clobazam	20	20	30	Media
Clonazepam	0,5-2	8	8	Alta
Clorazepato	15-20	20	60	Media
Clotiazepam	5-10	15	15	Media
Cloxazolam	1-2	9	4	Media
Diazepam	10	10	40	Media
Ketazolam	15-30	30	60	Media
Loflazepato	1-2	2	3	Media
Lorazepam	1-2	2,5	6	Alta
Nordiazepam	10-20	15	15	Media
Oxazepam	20	50	120	Baja
Prazepam	10-20	30	60	Media
Tetrazepam	20-50	100	150	Baja
Flunitrazepam	0,5-1	1	1	Alta
Flurazepam	15-30	30	30	Media
Loprazolam	1-2	1	1	Alta
Lormetazepam	1-2	1	2	Media
Nitrazepam	5-10	5	10	Media
Temazepam	20	20	20	Baja
Triazolam	0,25-0,5	0,25	0,25	Alta
Midazolam (I.V)	5-7,5	20	20	Alta

1.1.3 Efectos terapéuticos

Las benzodiazepinas han sido utilizadas durante décadas como hipnótico-sedantes en el tratamiento de la ansiedad, la epilepsia, el insomnio y otros trastornos (26).

A día de hoy se están llevando a cabo investigaciones en busca de nuevas indicaciones de las benzodiazepinas en neuropsiquiatría, por ejemplo, en alivio del dolor o en el tratamiento de la depresión (27, 28).

Todas las benzodiazepinas comparten propiedades farmacológicas similares, incluyendo sedación, relajación muscular, efectos anticonvulsivantes, hipnóticos y ansiolíticos (29). No obstante, cada benzodiazepina tiene una afinidad diferente por los distintos subtipos de receptores $GABA_A$, mostrando así distintos perfiles terepéuticos.Por ejemplo, algunas benzodiazepinas son más efectivas que otras como anticonvulsivantes (30), siendo diazepam y lorazepam utilizadas para el tratamiento de crisis epilépticas; mientras que clonazepam, clobazam y clorazepato se utilizan con más frecuencia como tratamiento preventivo (31). Otras benzodiazepinas, como lormetazepam, son más utilizadas por sus efectos hipnóticos (32). Por otra parte, las benzodiazepinas no están consideradas como tratamiento de primera elección en Trastornos depresivos del ánimo ni en Trastornos de ansiedad (33, 34, 35). Sin embargo, son un tratamiento de apoyo como hipnótico y ansiolítico (36, 37).

Las benzodiazepinas autorizadas, en España, a día de hoy, como ansiolíticos e hipnóticos se muestran en la tabla 4.

Tabla 4. Benzodiazepinas comercializadas en España como ansiolíticos e hipnóticos.

FÁRMACO	MEDICAMENTO®
Alprazolam	EFG, Trankimazin, Trankimazin retard
Bentazepam	Tiadipona
Bromazepam	EFG, Lexatin
Brotizolam	Sintonal
Clobazam	Noiafren
Clorazepato dipotásico	EFG, Tranxilium
Clordiazepóxido	Huberplex
Diazepam	EFG, Diazepam Normon, Diazepan Leo, Diazepan Prodes, Stesolid, Valium
Flurazepam	Dormodor
Ketazolam	Sedotime
Loprazolam	Somnovit
Lorazepam	EFG, Lorazepam Desgen, Lorazepam Vir, Orfidal, Placinoral
Lormetazepam	EFG, Aldosomnil, Loramet, Noctamid
Midazolam	Dormicum
Pinazepam	Duna
Quazepam	Quiedorm
Triazolam	Halcion

1.1.4 Efectos secundarios

A parte de los efectos terapéuticos deseados, las benzodiazepinas presentan una serie de efectos no deseados. Aunque actúen de forma rápida, su uso puntual puede producir efectos agudos como somnolencia, fatiga, estupor, alteraciones en la atención y concentración, apatía e hipotonía (38, 39). Además, su uso continuado produce efectos indeseables a medio y largo plazo como son la aparición de dependencia, alteraciones cognitivas y síndrome de abstinencia (40, 41, 42). Además, los resultados de un estudio reciente demuestran una mayor tasa de anhedonia en pacientes que utilizan benzodiazepinas frente a pacientes que no toman este tipo de fármacos (43).

Estos fármacos se utilizan frecuentemente en personas mayores, produciendo en ellos con mayor frecuencia efectos adversos como confusión, amnesia, ataxia y un mayor riesgo de caídas (44, 45). Existe una relación clara entre dosis altas de benzodiazepinas y caídas en personas de avanzada edad, debido a las alteraciones producidas sobre el estado de alerta y el equilibrio (46), incluso a dosis menores a las utilizadas habitualmente en población joven (47, 48). Además, un estudio reciente, realizado en una muestra de 1389 personas entre 60 y 70 años, sugiere que el uso prolongado de benzodiazepinas es un factor de riesgo independiente para el desarrollo de deterioro cognitivo en la tercera edad (49).

Por otra parte, las benzodiazepinas tienen potencial teratógeno, pudiendo producir malformaciones congénitas como hendiduras orofaciales. Por ello, están contraindicadas, especialmente, durante el primer trimestre del embarazo [categoría C de la Food and Drug Administration (FDA)] (50). Además, las benzodiazepinas están contraindicadas en casos de crisis de miastenia gravis, glaucoma del ángulo cerrado o insuficiencia respiratoria grave. Además se recomienda evitar su uso en casos de síndrome de apnea obstructiva del sueño, insuficiencia hepática grave y pacientes con deterioro cognitivo (5).

Los barbitúricos fueron desbancados por las benzodiazepinas al ser menos peligrosas frente a una sobredosis, ya que actúan produciendo un sueño prolongado pero sin deprimir peligrosamente la respiración ni la función cardiovascular (5). Sin embargo, es importante conocer que la utilización de benzodiazepinas junto con otros depresores del SNC, especialmente el alcohol, puede producir una depresión respiratoria grave y el consiguiente riesgo de perder la vida (5).

Existe un antídoto de las benzodiazepinas que contrarresta sus efectos de forma rápida y eficaz. Se trata del flumazenilo. Este fármaco se administra por vía intravenosa y se utiliza para revertir sospechas de sobreingesta o sobredosificación de benzodiazepinas, en reanimación post anestesia y en estados de inconsciencia de origen desconocido, debido a su rápida respuesta de 1-2 min tras la administración (51).

1.1.4.1 Síndrome de abstinencia

El síndrome de abstinencia a benzodiazepinas puede aparecer con su uso continuado durante escasos días o semanas. En general a menor semivida plasmática menor tiempo de uso requieren para producir un síndrome de abstinencia y más intenso es el mismo (52, 53).

La forma leve de este síndrome produce efecto rebote, sobretodo ansiedad, insomnio y trastornos del sueño. Son frecuentes otros trastornos como la pérdida de apetito, visión borrosa, boca seca, tinnitus, somnolencia y trastornos de la percepción como la hiperacusia y la fotofobia (54, 55). De forma más grave, puede producir tensión muscular, debilidad, espasmos, dolor, sudoración, escalofríos, alteraciones sensitivas y trastornos psiquiátricos como crisis de pánico, agitación, depresión y trastornos severos del sueño. La forma más grave de este síndrome se caracteriza, además, por ideación delirante, alucinaciones y síntomas de despersonalización (56, 57).

Para evitar sufrir el síndrome de abstinencia se recomienda retirar gradualmente las benzodiazepinas, bajando la dosis progresivamente. Se debe reducir una octava parte de la dosis cada quince días si las benzodiazepinas tienen una vida media larga (5). Otra alternativa utilizada consiste en sustituir la benzodiazepina utilizada por diazepam a dosis equivalente; cada quince días se reduce la dosis entre 2-2,5 mg. En caso de aparición de algún síntoma de abstinencia en la retirada, se debería mantener esa dosis hasta que mejoren dichos síntomas. En el caso en que no se pudiera realizar estos tipos de desescalada se puede valorar incorporar beta-bloqueantes como coadyuvantes, minimizando los síntomas del síndrome de abstinencia. En determinados casos donde aparezcan episodios intensos de depresión y ansiedad se puede añadir un antidepresivo al tratamiento (5).

1.1.5 Dependencia, Tolerancia y Abuso

Estudios recientes muestran que aproximadamente la mitad de los pacientes tratados con benzodiazepinas, durante un periodo de tiempo mayor a un mes, sufren un síndrome de dependencia (58). Otros estudios sugieren que entre el 58% y el 100% de las dosis terapéuticas utilizadas pueden producir dependencia física (59).

El uso de benzodiazepinas durante una o dos semanas, y a dosis moderadas, normalmente no produce los efectos de dependencia, tolerancia o síndrome de abstinencia, aunque sí se hayan descrito casos de insomnio de rebote (60). La dependencia puede producirse a dosis terapéuticas (61) y de forma característica puede ocurrir en ausencia de tolerancia y la tolerancia puede desarrollarse sin ninguna manifestación de dependencia (21, 62).

El diagnóstico de síndrome de dependencia requiere al menos tres de los siguientes criterios:

- Fuerte deseo de tomar la sustancia.
- Dificultad para controlar el uso de la sustancia.
- Sintomatología de síndrome de abstinencia.
- Evidencia de tolerancia.
- No disfrutar de otros intereses o placeres.

Existe una sólida base científica que demuestra una fuerte asociación entre el uso de benzodiazepinas de vida media corta y el riesgo de dependencia (58). La dependencia a benzodiazepinas supone una alteración del comportamiento que se puede caracterizar por buscar diferentes proveedores de recetas, falsificar recetas o bien obtener la medicación de diferentes farmacias (63, 54).

1.1.5.1 Tolerancia

La tolerancia se produce cuando el paciente presenta una menor sensibilidad al fármaco tras una exposición prolongada. A nivel celular, la tolerancia está producida por cambios en el intercambio intracelular de los receptores GABA, mientras que una exposición prolongada induce alteraciones selectivas de las subunidades de los receptores GABA a niveles de proteínas y del ácido ribonucleico mensajero (ARNm) (64). En modelos preclínicos, la administración crónica de benzodiazepinas produjo tolerancia secundaria a una menor expresión en el número de receptores GABA, produciendo una disminución de la sensibilidad a las benzodiazepinas (12, 65, 66, 67).

La tolerancia a los efectos hipnóticos aparece tras días y semanas mientras que a los efectos míorelajantes a las semanas y a los efectos anticonvulsivantes y ansiolíticos a los meses (59, 68, 69, 70, 71).

1.1.5.2 Abuso

El abuso de sustancias o fármacos es un patrón desadaptativo que se manifiesta con efectos adversos significativos y recurrentes relacionados con el uso repetido de dichas sustancias o fármacos (72). El abuso puede provocar tolerancia y dependencia.

Estudios poblacionales en diferentes países demuestran que entre un 4 y un 14.5% de los pacientes tratados con benzodiazepinas sufren abuso cuando se utilizan durante un periodo igual o mayor a 12 meses (73, 74, 75).

La benzodiazepina que presenta un mayor riesgo de abuso es el alprazolam (76, 77) y clínicamente está asociado a episodios amnésicos y alteraciones de memoria (78).

1.1.6 Interacción con otros fármacos

Las isoenzimas citocrómicas catalizan el metabolismo de las benzodiazepinas. Existen muchos fármacos que inducen o inhiben estas isoenzimas. Estos, a su vez, pueden interaccionar directamente con las benzodiazepinas. El alcohol y los

medicamentos opiáceos, antipsicóticos, antidepresivos, antihistamínicos y antiepilépticos interaccionan con las benzodiazepinas, haciendo que su efecto sedante aumente (79, 80, 81).

Los barbitúricos, antipsicóticos, hipnóticos, ansiolíticos, sedantes, antidepresivos, analgésicos narcóticos, antiepilépticos, anticonvulsivantes, anestésicos y antihistamínicos sedantes, en combinación con las benzodiazepinas pueden aumentar el efecto depresor sobre el SNC (82).

La concentración en sangre de las benzodiazepinas puede aumentar cuando se toman con fármacos que pueden inhibir las reacciones que catalizan los isoenzimas del citocromo. Estos fármacos son antibióticos macrólidos, antimicóticos, inhibidores selectivos de la recaptación de serotonina y la cimetidina. Sustancias como la carbamazepina, la fenitoína o el fenobarbital pueden reducir, drásticamente, la semivida de las benzodiazepinas, ya que son inductores enzimáticos (79).

Las benzodiazepinas reducen la eficacia de los fármacos antidepresivos. Esto se produce porque las benzodiazepinas reducen la neuroplasticidad, la capacidad que tiene el sistema nervioso de modificarse para formar conexiones nerviosas nuevas en respuesta a diferentes estímulos (83). Otros fármacos que interaccionan con las benzodiazepinas son los anticonceptivos orales, inhibiendo la actividad enzimática y reduciendo el aclaramiento renal (84). Finalmente, los efectos sedantes producidos por las benzodiazepinas pueden verse reducidos al administrarse conjuntamente con estimulantes como teofilina (85).

1.1.7 Costes socioeconómicos del uso prolongado de benzodiazepinas

El promedio de benzodiazepinas prescritas en atención primaria en la Región de Murcia (Tabla 5) fue de 68,4 y de 67,2 dosis diarias definidas (DDD) por cada 1.000 habitantes en los años 2016 y 2017, respectivamente (86).

Tabla 5. DDD de benzodiazepinas por cada 1000 habitantes, prescritas en atención primaria, divididas por áreas de salud de la Región de Murcia.

ÁREA DE SALUD	2015	2016	2017	2018
Área I - Murcia Oeste	68.8	69	68.6	68.1
Área II – Cartagena	81.4	82.1	81.9	83
Área III – Lorca	60.4	61.2	59.7	60.2
Área IV – Noroeste	75.3	77.8	75.9	76.4
Área V – Altiplano	52.4	51.9	49.8	48.3
Área VI - Vega Media del Segura	68.2	68.6	66.6	65.6
Área VII - Murcia Este	61.7	61.5	60.8	60.2
Área VIII - Mar Menor	54.2	51.8	49.5	47.3
Área IX - Vega Alta del Segura	79.1	83.5	81.7	82
Servicio Murciano de Salud	68	68.4	67.2	67

Según la Agencia Española de Medicamentos y Productos Sanitarios (AEMPS) el consumo de benzodiazepinas de perfil hipnótico (Figura 3) ha aumentado entre los años 2010 y 2020 en España (87). En 2010, la DDD fue de 20,716 por cada 1.000 habitantes mientras que en 2020 fue de 25,131. No obstante, la tendencia en el consumo de benzodiazepinas de perfil ansiolítico (Figura 4) ha sido irregular en España.

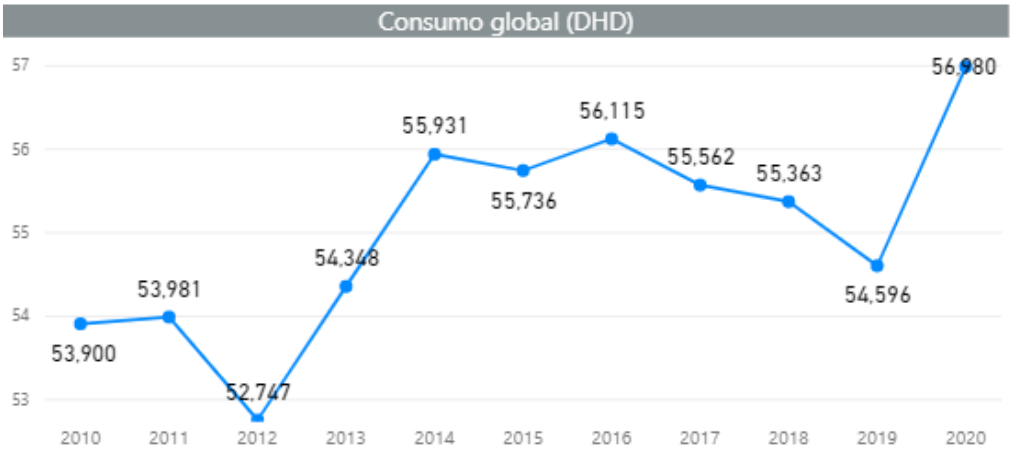

Figura 3. Promedio de DDD de benzodiazepinas hipnótico-sedantes por cada 1.000 habitantes entre los años 2010 y 2020 en España.

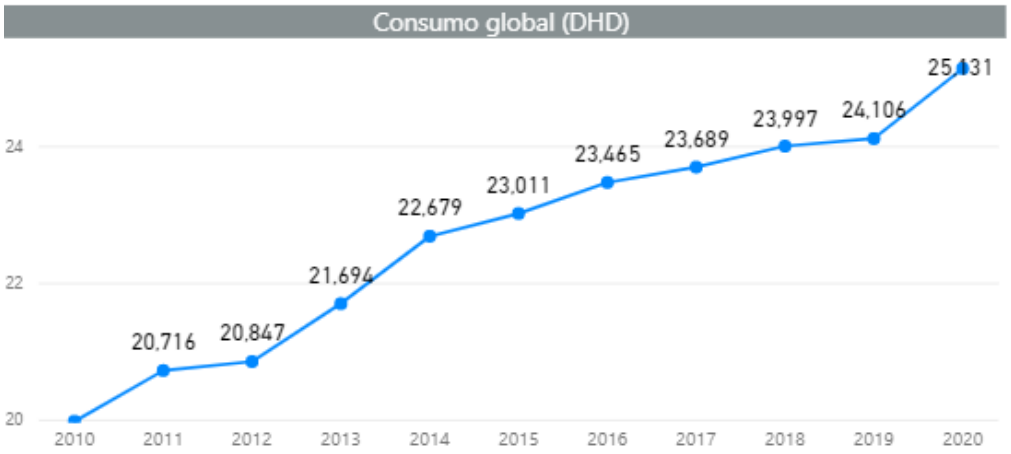

Figura 4. Promedio de DDD de benzodiazepinas ansiolíticas por cada 1.000 habitantes entre los años 2010 y 2020 en España.

Un estudio realizado en España con una muestra de 140 pacientes, cifra el coste sanitario asociado a las caídas sufridas por 57 pacientes que tomaban benzodiazepinas en 11.991€. De estos, 33 pacientes tuvieron que ser hospitalizados, lo que produjo un

coste total de 154.581€ (88). A nivel europeo, el coste económico asociado con fracturas por caídas relacionadas con el uso de benzodiazepinas (90% de las caídas producidas en ancianos) se estima entre 150 y 220 mil millones de euros al año (89).

Entre 1991 y 2009 el gasto en benzodiazepinas, en Estados Unidos (EEUU), pasó de 131,6 millones de dólares a 171,1 millones. Teniendo en cuenta, además, que el precio de cada fármaco fue bajando un 64,4% de media a lo largo de ese periodo, el gasto en estos fármacos aumentó considerablemente (90). Además, según el Departamento de Salud Mental de EEUU, en 2008, hubo aproximadamente 272.000 urgencias relacionadas con uso de benzodiazepinas, de las cuales el 40% incluían, también, la toma de alcohol (91).

En Canadá, el gasto en benzodiazepinas ascendió a cerca de 100 millones de dólares en el año 2007 (92). Los resultados de un estudio realizado en 2009 sobre la población anciana de Quebec mostraron que el 7% de este grupo de población no estaban recibiendo una dosis adecuada de benzodiazepinas y que esto supuso un sobrecoste sanitario de 3.076$ más por paciente, en comparación con los pacientes que estaban recibiendo una dosis adecuada (93).

1.2 TRASTORNOS PSIQUIÁTRICOS

1.2.1 Trastornos del espectro afectivo

1.2.1.1 Trastorno Bipolar

El trastorno bipolar afecta a más del 1% de la población mundial, independientemente de la nacionalidad, raza o el estatus económico (94) y suele diagnosticarse en adultos jóvenes. Se trata de un trastorno crónico recurrente, caracterizado por alteraciones del estado de ánimo en el que aparecen episodios maníacos o hipomaníacos alternados con episodios de depresión (95, 94). Detectar los episodios hipomaníacos y evaluarlos a lo largo del tiempo es clave para diferenciar este trastorno de otros que pudieran tener síntomas relacionados (95).

Además, el trastorno bipolar es una de las principales causas de discapacidad entre los jóvenes, produciendo deterioro funcional y afectando a la calidad de vida del enfermo (96, 97, 98). Con frecuencia, suelen aparecer antes y en mayor proporción que en la población general enfermedades cardiovasculares, diabetes, obesidad así como deterioro cognitivo y físico (99, 100).

Por otra parte, se estima que entre el 33% y el 50% de los enfermos con trastorno bipolar intentan suicidarse, al menos, una vez. Y, aproximadamente, entre el 15% y el 20% de los intentos acaban en un desenlace fatal (101).

El tratamiento farmacológico utilizado para tratar a pacientes con trastorno bipolar consta de fármacos antipsicóticos, antidepresivos y estabilizadores del ánimo (95).

1.2.1.2 Trastorno de ansiedad

El trastorno de ansiedad se caracteriza por presentar ansiedad y preocupación crónica acompañadas de síntomas físicos y psicológicos inespecíficos, como inquietud, fatiga, irritabilidad, tensión muscular, dificultad de concentración y trastornos del sueño (102).

El 6% de la población sufre, a lo largo de su vida, trastorno de ansiedad (103), siendo dos veces más frecuente en mujeres que en hombres (104).

Más de la mitad de los pacientes con trastorno de ansiedad tiene comorbilidades como depresión, trastornos de pánico (104). Los pacientes que sufren trastornos de ansiedad tienen un mayor riesgo de sufrir suicidios (105) y tienen más probabilidades de sufrir un evento cardiovascular adverso (106, 107).

El tratamiento de primera línea del trastorno de ansiedad son los inhibidores de recaptación de serotonina. La segunda línea farmacológica corresponde a las benzodiazepinas y anticonvulsivantes, como la pregabalina (108). Otros fármacos empleados en casos refractarios son los antipsicóticos como la quetiapina y la risperidona (109, 110), antihistamínicos como la hidroxizina (111) y antidepresivos tricíclicos como la imipramina (112).

1.2.1.3 Depresión

La Organización Mundial de la Salud (OMS) estima que los trastornos depresivos tienen una prevalencia del 16% de la población general (113). El trastorno depresivo se caracteriza por presentar tristeza, falta de interés, pérdida de placer e irritación; todo ello acompañado por cambios cognitivos y somáticos (114, 115).

Los trastornos depresivos se diferencian por su nivel de gravedad y duración entre leves, moderados y graves. Entre el 20 y 30% de los trastornos depresivos son crónicos (116, 117). La depresión es uno de los trastornos psiquiátricos más prevalentes e incapacitantes (118).

Los pacientes que sufren trastornos depresivos presentan más probabilidades de sufrir otras enfermedades crónicas y tienen menor adherencia al tratamiento (113).

Existe una estrecha relación entre la depresión y la ansiedad. De hecho, más del 50% de los pacientes con depresión presentan ansiedad y tienen mayor rechazo a los tratamientos que los pacientes con depresión pero sin ansiedad (119).

El tratamiento farmacológico de los trastornos depresivos consta de fármacos antidepresivos, antipsicóticos y en determinados casos se utilizan benzodiazepinas o litio (120, 121).

1.2.2 Trastornos del espectro psicótico

Los trastornos psicóticos son aquellos que presentan síntomas psicóticos, es decir, disfunciones cognitivas o perceptivas, principalmente delirios o alucinaciones. Se diferencian entre sí, dependiendo de su causa, duración, perfil sintomatológico y la relación entre los síntomas y los episodios de alteración del ánimo. El tratamiento de primera línea de todos ellos son los fármacos antipsicóticos. Otros fármacos utilizados son los antidepresivos, los estabilizadores del ánimo y las benzodiazepinas (122).

1.2.2.1 Psicosis aguda

La psicosis aguda es un trastorno caracterizado por tener un inicio y final conocidos e incluye síntomas psicóticos, afectivos y motores (123). Su prevalencia es de 3,9-9,6 de cada 100.000 personas en Europa (124, 125).

El inicio suele presentarse en un curso de pocas semanas con ideación delirante, pudiendo estar asociado a episodios de estrés agudo. El episodio puede ser desencadenado por un evento estresante o bien desarrollarse sin motivo aparente. Cuando la psicosis aguda se mantiene en el tiempo, pueden desarrollarse otros tipos de trastornos psicóticos como el trastorno bipolar o la esquizofrenia (126).

1.2.2.2 Esquizofrenia

Cerca del 1% de la población mundial padece esquizofrenia, con una prevalencia similar en diferentes países y sin diferencias de raza o sexo (127, 128). La enfermedad suele aparecer entre los 16-30 años y aunque no se ha establecido una causa genética, existen al menos siete genes que han demostrado tener relación con la enfermedad (129, 130). Se trata de un trastorno psicótico crónico que presenta síntomas psicóticos, tanto positivos como negativos, y deterioro cognitivo (131).

- Los síntomas psicóticos positivos incluyendelirios, alucinaciones y comportamientos extraños o inadecuados (132).

- Los síntomas negativos producen un estado de pobreza afectiva y conductual e incluyen anhedonia, apatía o inexpresividad (132).

- El deterioro cognitivo en la esquizofrenia repercute en la atención, concentración, función psicomotora, aprendizaje, memoria y en las función ejecutiva (132).

La esquizofrenia es una de las enfermedades mentales que mayor discapacidad producen en todo el mundo, a nivel sociolaboral, funcional y del autocuidado (132). Además, los pacientes que sufren esquizofrenia tienen mayor uso de tabaco, alcohol y drogas (133, 134), presentan más enfermedades infecciosas (135), respiratorias y cardiovasculares (136), presentan trastornos de estrés post-traumático (137), inestabilidad familiar e indigencia (138) y sufren ansiedad, depresión y hostilidad (139, 140, 141). El resultado de todos estos problemas asociados a la esquizofrenia aumenta el riesgo de mortalidad. Además, el 5% de los pacientes con esquizofrenia se suicidan (142).

1.2.2.3 Trastorno esquizoafectivo

El trastorno esquizoafectivo es una es una enfermedad mental, de inicio en adultos jóvenes, sin diferencia entre sexos, que presenta síntomas psicóticos y síntomas afectivos (102, 143). Estos pacientes sufren episodios de alucinaciones o ideas delirantes en contexto de un estado de ánimo alterado bien depresivo o bien maniaco (144).

Los síntomas que presentan los enfermos con trastorno esquizoafectivo pueden ser muy variados, tanto en gravedad, como en frecuencia. Esta gran variabilidad hace que el diagnóstico y el tratamiento sean muy complejos (145, 146).

Los diferentes episodios que ocurren en la vida de los pacientes con trastorno esquizoafectivo pueden producir un importante impacto en su calidad de vida y tienen un gran riesgo de sufrir ciertas comorbilidades, como el trastorno por abuso de sustancias, el síndrome metabólico y trastorno de ansiedad (147, 147, 149, 150).

1.2.2.4 Trastorno delirante

La prevalencia del trastorno delirante es del 0,2% (102). La enfermedad suele iniciarse sobre los 40 años, aunque el rango va entre los 18 y los 90 años (151). Suele presentarse más comúnmente en mujeres que en hombres (152). Este trastorno se caracteriza por presentar episodios de ideas delirantes durante, al menos, un mes. Estos delirios no tienen ninguna causa subyacente aparente, ni médica, ni psicológica ni tóxica. Los delirios más frecuentes son de tipo celotipia, erótico-maníaco, grandiosidad, persecutorio, somático y paranoide (153).

El tratamiento farmacológico para el trastorno delirante utiliza fármacos antipsicóticos, antidepresivos y estabilizadores del ánimo aunque su eficacia es limitada (154).

1.2.3 Trastornos de personalidad

La prevalencia estimada, en diferentes países, de los trastornos de personalidad es de un 6,1% (155). Además, algunos estudios sugieren que entre el 9-14,8% de los pacientes psiquiátricos presentan, al menos, un trastorno de personalidad (156, 157).

Los trastornos de la personalidad son manifestaciones mentales extremas que interfieren en la vida diaria de los enfermos, presentando comportamientos, emociones y pensamientos que son muy diferentes a los esperados en su cultura (158).

Los trastornos de personalidad están asociados a una calidad de vida menor, interfiriendo en las relaciones interpersonales, en el trabajo y en otros ámbitos de la vida diaria, provocando, además, una mayor mortalidad.

Existen diferentes tipos de trastornos de personalidad, siendo el trastorno límite de personalidad el más representativo, presentando una prevalencia del 1,6% (156). Este trastorno de personalidad se caracteriza por presentar inestabilidad en las relaciones interpersonales y en la relación propia del individuo, presentando mucha impulsividad (102).

A pesar de que no existe ningún tratamiento farmacológico indicado para estos pacientes, el uso de psicofármacos es habitual para manejar los diferentes síntomas psiquiátricos que sufren (159).

1.3 OTROS PSICOFÁRMACOS

1.3.1 Fármacos antipsicóticos

El grupo de fármacos antipsicóticos fue desarrollado a partir de los años ’50 del siglo XX (160). Los perfiles farmacológicos y terapéuticos de estos fármacos son muy similares entre sí. Aunque su indicación principal es el tratamiento de síntomas psicóticos, otras indicaciones incluyen náuseas, émesis, hipo, prurito y dolor crónico (5).

1.3.1.1 Clasificación de los fármacos antipsicóticos

La familia de los fármacos antipsicóticos puede dividirse en dos grupos: a) antipsicóticos típicos o de primera generación y b) atípicos o de segunda generación.

Tabla 6. Clasificación de los fármacos antipsicóticos.

Fármacos antipsicóticos de primera generación	Fármacos antipsicóticos de segunda generación
Clorprimazina	Amisulpirida
Levomepromazina	Clozapina
Flufenazina	Olanzapina
Perfenazina	Paliperidona
Periciazina	Quetiapina
Haloperidol	Risperidona
Droperidol	Sertindol
Pimozida	Ziprasidona
Zuclopentixol	Aripiprazol
Flupentixol	Sulpirida
	Tiaprida
	Clotiapina
	Asenapina
	Loxapina
	Lurasidona
	Cariprazina

El mecanismo de acción de los antipsicóticos de primera generación consiste en el antagonismo de los receptores dopaminérgicos (D)2 pre-sinápticos y post-sinápticos (5, 161). Los antipsicóticos de segunda generación bloquean los receptores dopaminérgicos y serotoninérgicos (5, 161, 162). Al bloquear estos receptores mejoran los síntomas negativos y disminuye la frecuencia de efectos extrapiramidales (163). Existe algún fármaco, como aripiprazol cuyo mecanismo de acción es el agonismo parcial sobre receptores D2 y 5-hidroxitriptamina (5-HT)$_{1A}$ y antagonismo de receptores 5-HT$_2$ (164).

1.3.1.2 Efectos secundarios

Todos los fármacos antipsicóticos, tanto los de primera como los de segunda generación producen efectos adversos en mayor o menor medida.

a) Efectos extrapiramidales

Los antipsicóticos de segunda generación producen menor frecuencia de efectos extrapiramidales (165). Al bloquear los receptores D2 de la vía nigroestriada, los antipsicóticos pueden producir: temblor, discinesia, acatisia e incluso el síndrome neuroléptico maligno (166, 167). También puede aparecer discinesias tardias, es decir, tras meses o años de la ingesta del fármaco durante al menos 3 meses. Su prevalencia es del 20-35% (168). Son movimientos anormales crónicos localizados en el tronco y las

extremidades, aunque principalmente se localizan en la zona facial o bucolingual (169). Además, el bloqueo de los receptores dopaminéricos a nivel tuberoinfundibular puede producir una elevación de los niveles de prolactina (167).

b) Sedación

La sedación es uno de los efectos más frecuentes (170, 171), especialmente con antipsicóticos típicos. Es más frecuente e intensa en las primeras fases del tratamiento y la mayoría de los pacientes desarrolla cierta tolerancia (5).

c) Efectos anticolinérgicos y antiadrenérgicos

El bloqueo de receptores colinérgicos puede producir: sequedad de boca, secreciones bronquiales y sudoración, visión borrosa, estreñimiento, taquicardia y retención urinaria (172). A largo plazo, el bloqueo de receptores colinérgicos puede producir deterioro cognitivo, confusión, delirio, somnolencia y alucinaciones (5).

Entre los efectos antiadrenérgicos es frecuente la aparición de congestión nasal, mareo e hipotensión ortostática (5, 173).

- Efectos endocrinos:

Los antipsicóticos se han relacionado con el desarrollo de resistencia a la insulina y diabetes (174). Además, favorecen la aparición de dislipemia (175) y aumento de peso, con más frecuencia los de primera generación (167, 176). En particular, un estudio reciente ha demostrado que la administración de antipsicóticos durante diez semanas produce una ganancia ponderal de entre 1-4 kg de peso (177). Además, entre el 20-40% de los pacientes tratados con fármacos antipsicóticos desarrolla hiperprolactinemia, siendo más frecuente en mujeres que en hombres (178, 179, 180). Con menor frecuencia pueden producir: disfunción eréctil, alteraciones en la eyaculación, pérdida de libido y anorgasmia (5, 181).

d) Otros efectos secundarios

Los fármacos antipsicóticos pueden producir hepatitis (182). A nivel cardiovascular, pueden causar arritmias siendo más frecuente la prolongación del intervalo QT (183, 184). Además, los antipsicóticos diminuyen el umbral convulsivo por lo que pueden desencadenar crisis epilépticas (5). Por último, el uso de clozapina puede producir efectos hematológicos muy poco frecuentes pero graves como agranulocitosis, eosinofilia, trombocitopenia y anemia (185, 186, 187).

1.3.1.3 Fármacos antipsicóticos inyectables de larga duración (LAIs)

Las formulaciones inyectables de fármacos antipsicóticos de primera generación se desarrollaron en la década de 1960, incorporaban la molécula del fármaco esterificado a un vehículo consistente de aceite de sésamo (188).

El medicamento inyectable de risperidona (Figura 5) está formulado con esferas de ácido glicólico poliláctico y está diseñado para una administración cada dos semanas (189, 190). Debido a que la liberación del fármaco se va haciendo progresivamente, es necesario complementar el tratamiento con risperidona por vía oral durante los primeros veintiún días (191, 192).

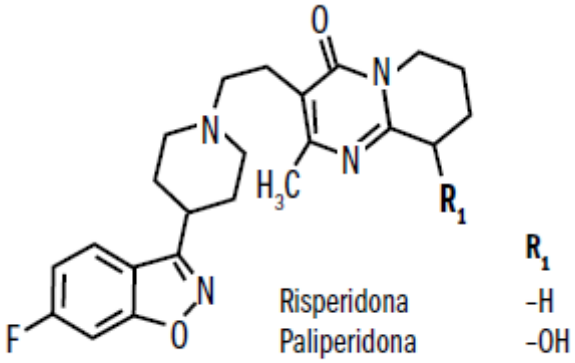

Figura 5. Estructura química de la risperidona y paliperidona.

El pamoato de olanzapina (Figura 6) es una sal cristalina micronizada en una formulación monohidrato. Esta medicación se puede administrar cada 2 o 4 semanas sin necesidad de complementar con dosis oral, a no ser que fuera necesario por las características del paciente o por la farmacoterapia elegida (189, 193).

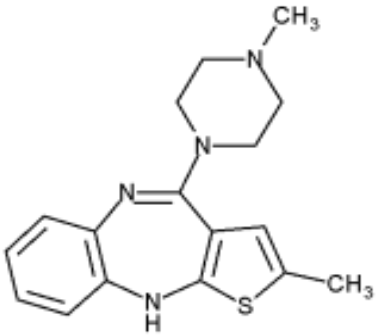

Figura 6. Estructura química de la olanzapina.

El palmitato de paliperidona (Figura 5) utiliza tecnología Nanocrystal® para sus dos formulaciones inyectables, tanto para la mensual como para la trimestral (189, 194). La formulación trimestral tiene nanocristales más grandes que los de la formulación

mensual, dando lugar a concentraciones de fármaco en suero más sostenidas y prolongadas (195).

Existe una formulación mensual de aripiprazol (Figura 7), formulada con monohidrato polimórfico en base acuosa, que posee un bajo peso molecular (189, 196) y otra formulación inyectable que utiliza un profármaco, aripiprazol lauroxil y posee un mayor peso molecular (189, 196). Después de la administración intramuscular el aripiprazol lauroxil se transforma en N-hidroximetil aripiprazol y después en aripiprazol (197). Las diferentes formulaciones inyectables hacen que la dosificación oral complementaria varíe entre los dos depósitos de aripiprazol. La formulación con monohidrato necesita catorce días de dosificación oral complementaria, mientras que la formulación con lauroxil necesita veintiún días, para llegar a la concentración adecuada de fármaco en sangre (198, 199).

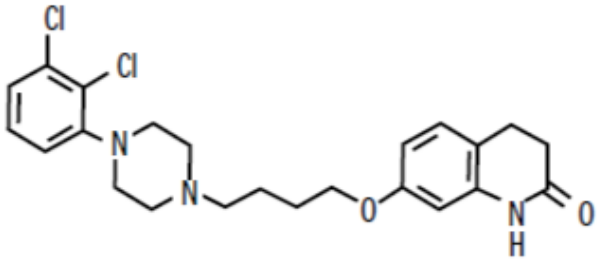

Figura 7. Estructura química del aripiprazol.

Se están desarrollando nuevas formulaciones que ayuden a aumentar el periodo entre administraciones del fármaco, como por ejemplo, implantes de risperidona para el tratamiento de la esquizofrenia que mantengan la dosis adecuada durante seis meses (200) y ya está en trámites de aprobación la paliperidona semestral (201).

En cuanto a los posibles efectos adversos de los LAIs duración son los propios asociados a los principios activos que contienen, añadiendo los posibles efectos asociados a la administración inyectable (195).

1.3.2 Fármacos antidepresivos

Los fármacos de la familia de los antidepresivos pueden mejorar el estado de ánimo del paciente y algunos de ellos tienen efecto sedante o analgésico (5).

Este grupo de fármacos, además de estar indicados como tratamiento de trastornos de ansiedad y depresión, también se utilizan para tratar otros procesos como insomnio, trastornos obsesivo-compulsivos, trastornos alimentarios, trastornos por abuso de sustancias, disfunción eréctil y algunos tipos de dolor neuropático (202, 203).

Los fármacos antidepresivos se clasifican según su meceanismo de acción en:

- Inhibidores selectivos de recaptación de serotonina (ISRS): Aumentan la concentración de serotonina en la hendidura sináptica al inhibir su recaptación por la membrana presináptica (204). Citalopram, escitalopram, sertralina, paroxetina, fluvoxamina, fluoxetina (Figura 8) y vortioxetina.

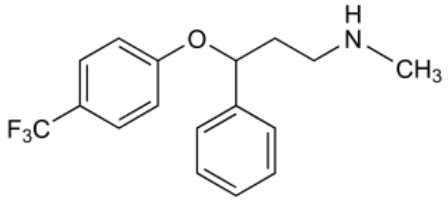

Figura 8. Estructura química de la fluoxetina.

- Inhibidores selectivos de recaptación se serotonina y noradrenalina (IRSN): Aumentan la concentración de serotonina y noradrenalina en la hendidura sináptica al inhibir su recaptación por la membrana presináptica (204).

Venlafaxina (Figura 9), desvenlafaxina y duloxetina.

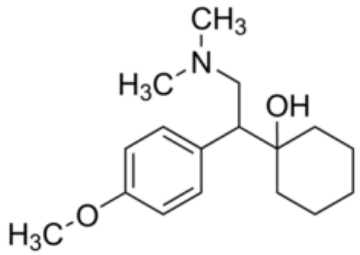

Figura 9. Estructura química de la venlafaxina.

Antidepresivos tricíclicos (ADT): Aumentan la concentración de serotonina y noradrenalina en la hendidura sináptica al inhibir su recaptación por la membrana presináptica (204). Sonfármacos cuya estructura química difiere en el anillo central. Poseen acciones variables sobre receptores adrenérgicos, colinérgicos e histaminérgicos.

Amitriptilina (Figura 10), clomipramina, tianeptina, nortriptilina, doxepina, imipramina y trimipramina.

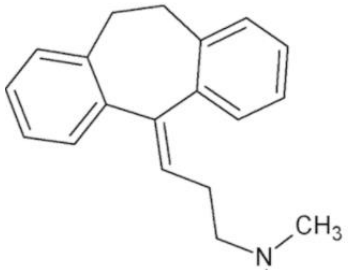

Figura 10. Estructura química de la amitriptilina.

- Antidepresivos noradrenérgicos o serotoninérgicos selectivos (NaSSA): Aumentan la concentración de serotonina y noradrenalina en la hendidura sináptica al inhibir su recaptación por la membrana presináptica (204).

Mirtazapina (Figura 11).

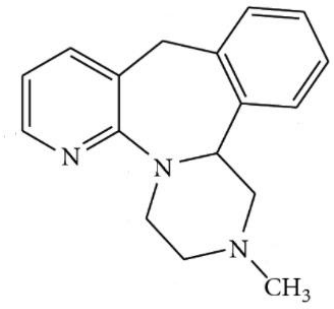

Figura 11. Estructura química de la mirtazapina.

- Inhibidores de la recaptación de dopamina y noradrenalina (IRDN): Aumentan la concentración de dopamina y noradrenalina en la hendidura sináptica al inhibir su recaptación por la membrana presináptica (204).

Bupropión (Figura 12).

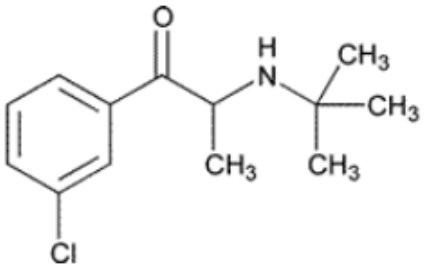

Figura 12. Estructura química del bupropión.

- Antidepresivos atípicos: Presentan ciclos en su estructura.La trazodona es antagonista del receptor 5-HT_{2A} de la serotonina e inhibidor de la recaptación de serotonina por la membrana presináptica (204).

Trazodona (Figura 13), mianserina, maptrotilina.

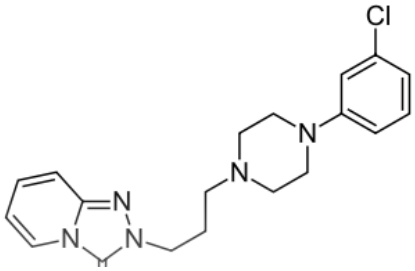

Figura 13. Estructura química de la trazodona.

- Agonistas melatoninérgicos: agonistas de los receptores de melatonina $(MT)_1$ y MT_2 y antagonista $5\text{-}HT_{2C}$.

Agomelatina (Figura 14).

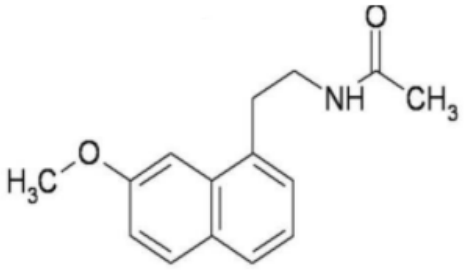

Figura 14. Estructura química de la agomelatina.

- Inhibidores selectivos de la recaptación de noradrenalina (IRNA): Aumentan la concentración de noradrenalina en la hendidura sináptica al inhibir su recaptación por la membrana presináptica (204).

Reboxetina (Figura 15).

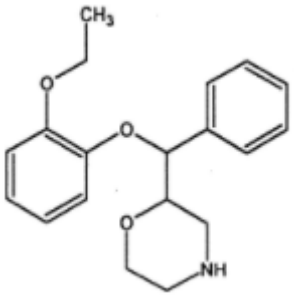

Figura 15. Estructura química de la reboxetina.

Los efectos adversos son más frecuentes y más característicos en aquellos grupos que interaccionan con receptores colinérgicos, como los antidepresivos triciclicos. Algunos estudios sugieren que un 43% de los pacientes tratados con antidepresivos no se adhieren al tratamiento debido a los efectos adversos (205). Entre otros efectos adversos pueden producir: sequedad de boca, retención urinaria alteraciones de la visión, disminución de la libido, disfunción eréctil, disminución/aumento de peso, bloqueos cardiacos, prolongación del intervalo QTc (206, 207, 208, 209).

1.3.3 Fármacos estabilizadores del ánimo

Los fármacos estabilizadores del ánimo o eutimizantes son los fármacos de primera línea en el tratamiento del trastorno bipolar, tanto para fases agudas, como de mantenimiento (5, 210).

El carbonato de litio es un estabilizador del ánimo esencial para el tratamiento del trastorno bipolar en fase depresiva (211). En combinación con otra terapia farmacológica, el litio previene, eficazmente, las recaídas y es muy eficaz en pacientes con alto riesgo de suicidio (212).

El valproato y la carbamazepina pueden ser eficaces en fases depresivas de trastorno bipolar, ayudando a disminuir los síntomas depresivos y reduciendo la probabilidad de recaída (213, 214). La eficacia de estos dos fármacos es menor en fases agudas de depresión en trastorno bipolar, como tratamiento de mantenimiento y para evitar recaídas, comparada con la eficacia del litio (215).

Muchas guías clínicas recomiendan la lamotrigina como primera línea terapéutica en fases depresivas leves y moderadas de trastorno bipolar (216, 217, 218, 219, 220, 221). La monoterapia con lamotrigina o combinada con litio o antipsicóticos está recomendada (212).

Los efectos adversos comunes a los fármacos estabilizadores del ánimo son: sedación excesiva, mareos o vértigo, ataxia, alteraciones cognitivas y visuales o molestias gastrointestinales como náuseas o vómitos (222). El uso del litio puede producir diabtes insípida, hipercalcemia, cansancio, debilidad muscular, fasciculaciones musculares, temblor, alteraciones de la repolarización cardiaca, hipotiroidismo, bocio, síntomas extrapiramidales. El uso de carbamazepina puede producir osteomalacia (223), el ácido valproico, osteopenia y fracturas osteoporóticas (223), el topiramato, pérdida de peso (224) y la lamotrigina erupciones cutáneas (222).

II- OBJETIVOS

II- OBJETIVOS

2.1 OBJETIVO PRINCIPAL

El objetivo general es estudiar los patrones de prescripción médica de benzdiazepinas en Salud Mental en la Región de Murcia y analizar el uso de estos fármacos en pacientes diagnosticados de diferentes enfermedades mentales.

2.2 OBJETIVOS ESPECÍFICOS

- Evaluar los factores de riesgo asociados al consumo de benzodiazepinas.

- Evaluar los patrones de prescripción y el uso de benzodiazepinas en enfermedades severas y comunes, así como entre enfermedades mentales con clara sintomatología psicótica y afectiva.

- Evaluar el posible impacto de los LAIs en el uso de benzodiazepinas en los pacientes con enfermedades mentales graves.

- Evaluar el posible impacto de los LAIs en el uso de benzodiazepinas en pacientes diagnosticados de esquizofrenia y trastorno de personalidad límite.

III- RESULTADOS

ORIGINAL RESEARCH

Key Words: benzodiazepines, prescription patterns, diazepam equivalents, mental health

Evaluation of Risk Factors Associated to Prescription of Benzodiazepines and its Patterns in a Cohort of Patients from Mental Health: A Real World Study in Spain

By Jorge Simal-Aguado, María-Pilar Campos-Navarro, Francisco Valdivia-Muñoz, Alejandro Galindo-Tovar, Juan Antonio García-Carmona

ABSTRACT ~ Purpose: *we aimed 1) to evaluate the risk factors associated to the benzodiazepines intake; 2) to assess the impact about the use of long acting injectables antipsychotics (LAIs); 3) to assess the risk in severe and affective disorders and 4) to identify the prescription patterns of use in mental health in a cohort of patients from Spain.* ***Methods:*** *735 outpatients from Mental Health were included. Demographic and clinical data were collected. In order to compare the use of benzodiazepines we calculated the daily dose equivalents (mg/day) to diazepam as standard.* ***Results:*** *The most commonly prescribed benzodiazepine was clonazepam (33%) and the mean daily dose of diazepam equivalents was 24.9 mg. It was higher in affective disorders (40.35 ± 3.36) and lower in patients using LAIs antipsychotics (17.50 ± 1.39; p = 0.001). Multivariate analysis showed that to be women (OR = 1.559, 95% CI = 1.059–2.295, p = 0.024), the use of drugs (OR = 1.671, 95% CI = 1.127–2.477, p = 0.011) and suffering any affective disorder (OR = 1.542, 95% CI = 1.355–1.826, p = 0.040) increased the risk of benzodiazepine intake. In contrast, the use of LAIs antipsychotics significantly reduced it versus oral antipsychotics (OR = 5.226, 95% CI = 3.185–8.575, p = 0.001).* ***Conclusions:*** *benzodiazepines are widely prescribed, mainly clonazepam followed by lorazepam and diazepam. Most of patients used at least one benzodiazepine and the mean daily intake was 25 mg diazepam equivalents. Therefore, benzodiazepines are extensively prescribed and used at higher doses than desirable. These, findings could be useful for clinicians and their practice.* Psychopharmacology Bulletin. *2021;51(1):81–93.*

Simal-Aguado, Galindo-Tovar, Department of Pharmacy, Health Sciences Faculty, San Antonio Catholic University of Murcia, UCAM, Murcia; Spain. Campos-Navarro, Unit of Acute Psychiatry, Santa Lucia University Hospital, Cartagena; Spain. Valdivia-Muñoz, Center of Mental Health Infante, Murcia; Spain, Center of Mental Health Cartagena, Cartagena, Murcia; Spain. Garcia-Carmona, Department of Neurology, Santa Lucia University Hospital, Cartagena; Spain, Unit of Acute Psychiatry, Reina Sofia University Hospital, Murcia; Spain.

To whom correspondence should be addressed: Juan Antonio García-Carmona; MD, PhD, BPharm, Department of Neurology, Santa Lucia University Hospital, C/Mezquita s/n, 30202, Cartagena, Murcia, Spain. Phone/Fax: +34 968 110 859; E-mail: dr.jagarcar@gmail.com ORCID ID: 0000-0003-3938-7698

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Introduction

The first benzodiazepine was the chlordiazepoxide developed in 1955 followed by the diazepam in 1963.[1] Since then, several molecules have been developed constituting a group of drugs exerting its anxiolytic, hypnotic, anticonvulsant and muscle relaxant effects through enhancing the effect of gamma-amynobutyric acid (GABA) at its $GABA_A$ receptor.[2,3]

Despite benzodiazepines being well known for its potential dependence syndrome and their common side effects (sedation, memory loss, falls)[4] their prescription and use is widely increasing. In this regard, a 113% increased use of benzodiazepines from 2000 to 2012 has been reported in Spain.[5] In this line, a recent survey in Spanish general population showed that the prevalence of use of benzodiazepines was 20.8% sometime and 5.9% daily, always highlighting a higher consumption in women (63%).[5] Studies in general population showed that the age is the most consistent predictor of taking benzodiazepines.[6,7] Likewise, the consumption of benzodiazepines has been shown to be higher in women than in men in general population.[8–10] In contrast, only few studies evaluated the use of benzodiazepines by using a cohort from mental health services.[11–13] Unfortunately, most of them focused in particular groups of risk such as substance of abuse users,[14] depressed patients[15] or whose diagnosed with schizophrenia and panic disorders.[16]

Therefore, the aim of this study was 1) to evaluate the risk factors associated to the benzodiazepines intake; 2) to assess the impact about the use of long acting injectables antipsychotics (LAIs); 3) to assess the risk in severe and affective disorders and 4) to identify the prescription patterns of use in mental health in a cohort of patients from the Region of Murcia, Spain.

Methods

Study Design

As previously described,[17] we designed a cross-sectional study, from 2015 to 2017, based on a representative sample of the adult and non-institutionalized population of Mental Health in the Region of Murcia. A total number of 735 patients, ⩾18 years old, were included if were previously diagnosed with a mental health disorder according to the DSM-V guidelines. Exclusion criteria included institutionalized patients, use of 2 LAIs, intellectual disability or autistic spectrum disorders and patients with missing records or unable to confirm treatment continuation during 1 year. The present study was drawn up

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following the 'STrengthening the Reporting of OBservational studies in Epidemiology' (STROBE) Statement ítems.[18]

Study Measures

Data collected included demographical information such as age, sex, civil status, tobacco and other drugs use as well as clinical data such as the disorder, its evolution (years), the benzodiazepines dosage as well as concomitant psychiatric medications, including the use of both, oral and long-acting injectable (LAIs) antipsychotics, antidepressants, mood stabilizers and biperiden. In order to compare the use of benzodiazepines we calculated the daily dose equivalents of benzodiazepines (mg/day) by diazepam as standard to compare the corresponding doses as previously published.[19]

Statistical Analysis and Confounding Factors

All analyses were performed using IBM SPSS Statistics version 21.0 (IBM Corp., Armonk, NY, USA). We expressed quantitative variables as means [± standard error media (SEM)] and categorical variables as numbers (percentage). We assessed normality of distributions using histograms and the Shapiro–Wilk test. Sample basal characteristics were analyzed by univariate analysis. Variables associated in the univariate analysis and variables with statistical trend ($p < 0.1$) were entered as factors in a bivariate logistic regression model to identify the variables independently associated to benzodiazepine intake. Student's t-test was used to assess differences in diazepam equivalents within groups by sex, use of LAIs or affective disorder. Differences with a p value <0.05 were considered significant.

Results

Sample basal characteristics are shown in Table 1. Patients taking benzodiazepines were more frequently women (70% versus 66% in men; $p = 0.006$), with shorter disease duration (10.9 ± 0.4 versus 13.0 ± 0.7 in no-users; $p = 0.035$) and used more frequently drugs (38% versus 22% in non-users; $p = 0.001$). The 87% and the 67% of patients diagnosed with a general or severe psychiatric disorder, respectively, were prescribed with benzodiazepines. Furthermore, the 81% of patients diagnosed with an affective disorder were prescribed with benzodiazepines while the 64% of patients diagnosed with no-affective disorders took benzodiazepines. Among LAIs users, the rate of benzodiazepines prescription was lower compared to no-LAIs users (62% vs. 86%, respectively).

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TABLE 1

Univariate Anaysis Between Users and Non-Users of Benzodiazepines

	TOTAL N = 735	NO BDZ N = 234	BDZ N = 501	*P*-VALUE
Sex (%)				0.006
Women	325 (44)	96 (41)	229 (49)	
Men	410 (56)	138 (58)	272 (51)	
Age (y ± SEM)	41.6 ± 0.5	41.7 ± 0.9	41.5 ± 0.5	0.305
Disorder duration (y ± SEM)	11.5 ± 0.4	13.0 ± 0.7	10.9 ± 0.4	0.035
Legal status (%)				0.140
Single/Divorced/Widow	563 (77)	158 (78)	405 (76)	
Coupled/Married	172 (23)	44 (22)	128 (24)	
Tobacco & Drugs (%)				
Tobacco	325 (44)	87 (43)	238 (45)	0.461
Other drugs	247 (33)	44 (22)	203 (38)	0.001
Mental Disorder				0.091
General Disorders	203 (28)	27 (13)	176 (33)	
Severe Disorders	532 (72)	175 (87)	357 (67)	
Affective Disorders				0.005
No	349 (47)	127 (63)	222 (42)	
Yes	386 (53)	75 (37)	311 (58)	
Use of LAI-antipsychotic				0.001
No	323 (44)	46 (23)	277 (52)	
Yes	412 (56)	156 (77)	256 (48)	

Affective disorders included depressive, anxiety-depressive, anxiety, schizoaffective, bipolar and personality disorders. Non-affective disorders included schizophrenia, psychosis, delusional disorders. BDZ = bendozdiazepines, LAI = long acting injectables antipsychotics, SEM = standard error mean.

We performed a logistic bivariate regression analysis to truly establish the factors independently associated with the intake of benzodiazepines. As shown in Table 2, bivariate logistic regression model showed that women had higher risk of benzodiazepine intake compared to men (OR = 1.559, 95% CI = 1.059–2.295, p = 0.024). Furthermore, the use of drugs (OR = 1.671, 95% CI = 1.127–2.477, p = 0.011) and suffering any affective disorder (OR = 1.542, 95% CI = 1.355–1.826, p = 0.040) increased the risk of benzodiazepines intake. In contrast, the use of LAIs antipsychotics significantly reduced the risk of benzodiazepines intake versus oral antipsychotics (OR = 5.226, 95% CI = 3.185–8.575, p = 0.001).

Diazepam Equivalents

The mean daily doses of benzodiazepines are shown in Figure 1 as diazepam equivalents. Mean daily dose of diazepam equivalents in our cohort was 24.9 mg (24.90 ± 1.42). As shown in A) student's t-test showed no

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TABLE 2

Risk Factors Associated to Benzodiazepine Intake by Bivariate Logistic Regression Model

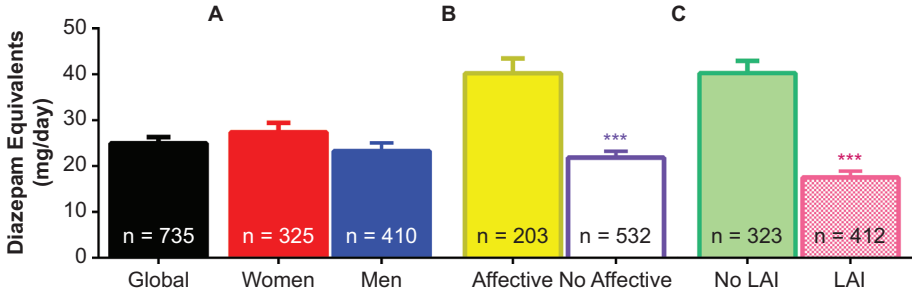
	OR	95% CI	*P*-VALUE
Sex			0.024
Women	1.559	1.059–2.295	
Men	1		
Disorder duration	0.999	0.980–1.018	0.894
Drugs use			0.011
No	1		
Yes	1.671	1.127–2.477	
Mental Disorder			0.175
General	1.433	0.852–2.411	
Severe	1		
Affective Disorder			0.040
No	1		
Yes	1.542	1.355–1.826	
Use of LAIs			0.001
No	5.226	3.185–8.575	
Yes	1		

LAIs = long acting injectable antipsychotics.

statistical differences between the daily dose of women and men (27.41 ± 2.04 and 23.29 ± 1.79, respectively). Nonetheless, as shown in B) and C), statistical differences were found between affective (40.35 ± 3.36) or no-affective disorders (21.98 ± 1.37, $\chi^2_{[df = 1,734]} = 6.06$; p = 0.001) as

FIGURE 1

Diazepam Equivalents by (A) Sex, (B) Affective vs No-Affective Disorders and (C) Long-Acting Injectable Use (LAIs)



Global column represents the mean data from the whole cohort of patients. Data are expressed as the mean ± SEM. Student's t-test revealed statistical differences between affective and no-affective disorders (***p = 0.001) as well as when comparing the use of oral versus LAIs (***p = 0.001) Abv: LAIs = long acting-injectables antipsychotics.

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well as when comparing the use of oral (40.25 ± 2.99) versus LAI antipsychotics (17.50 ± 1.39, $\chi^2_{[df = 1,734]} = 7.89$; $p = 0.001$).

Use of Benzodiazepines by Sex and Mental Disorder

As shown in Table 3, the most commonly prescribed benzodiazepine in both sexes was clonazepam in 33 and 32% of cases, followed by lorazepam (32% in women and 24% in men) and Diazepam (21% in women and 22% in men). Likewise, as shown in Table 4, patients diagnosed with a depressive-anxiety disorder were the more frequently prescribed with benzodiazepines (92%) followed by patients suffering from depression (88%) and schizoaffective disorder (79%). In contrast, a lower rate of patients with bipolar disorder took benzodiazepines (57%). Among psychotic disorders, 65% of patients with schizophrenia took benzodiazepines while only the 48% and 36% of patients with psychosis and Deliroid disorder, respectively. It worth to point out that about 75% of patients diagnosed with a personality disorder were prescribed with benzodiazepines. Most of patients used only one type of benzodiazepine (48%) and the 19% used 2 types. Nonetheless, the 44% and the 24% of patients diagnosed with anxiety-depressive and personality disorders, respectively, used two different benzodiazepines. Once again, clonazepam was the most used in the different disorders (mean 22%, range 4–30) excepting in deliroid, anxiety-depressive and depression disorders which more frequently were prescribed with lorazepam.

TABLE 3

Use of Benzodiazepines by Sex

	TOTAL N = 735	WOMEN N = 325	MEN N = 410
BDZs' users (%)	n = 501	n = 229	n = 272
1	353 (48)	159 (69)	194 (71)
2	127 (17)	60 (26)	67 (25)
3	21 (3)	10 (5)	11 (4)
BDZs (%)			
Alprazolam	27 (5)	12 (5)	15 (6)
Bromazepam	14 (3)	8 (3)	6 (2)
Clonazepam	164 (33)	76 (33)	88 (32)
Clorazepate	18 (4)	8 (3)	10 (4)
Diazepam	108 (22)	48 (21)	60 (22)
Flurazepam	96 (19)	40 (17)	56 (21)
Ketazolam	10 (2)	7 (3)	3 (1)
Lorazepam	139 (28)	74 (32)	65 (24)
Lormetazepam	94 (19)	48 (21)	46 (17)

BDZs = benzodiazepines.

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TABLE 4

Use of Benzodiazepines by Mental Disorder

	TOTAL N = 735	SCH N = 277	PSY N = 44	DELD N = 28	SCHAFF N = 90	BPD N = 93	PDS N = 112	DEPD N = 42	ADD N = 39	OTHERS N = 10
N benzodiazepines (%)	**501 (68)**	**181 (65)**	**21 (48)**	**10 (36)**	**71 (79)**	**53 (57)**	**83 (74)**	**37 (88)**	**36 (92)**	**9 (90)**
1	353 (48)	128 (46)	18 (41)	8 (29)	51 (57)	38 (38)	52 (45)	27 (64)	22 (56)	9 (90)
2	127 (19)	44 (16)	3 (9)	2 (7)	16 (18)	14 (19)	25 (24)	9 (21)	14 (44)	–
3	21 (3)	9 (3)	–	–	4 (4)	1 (1)	6 (5)	1 (3)	–	–
BDZs (%)										
Alprazolam	27 (4)	13 (5)	1 (2)	1 (4)	–	1(1)	7 (6)	2 (5)	1 (3)	1 (10)
Bromazepam	14 (2)	5 (2)	1 (2)	–	2 (2)	2 (2)	2 (2)	2 (5)	–	–
Clonazepam	164 (22)	59 (21)	7 (16)	1 (4)	27 (30)	22 (24)	27 (24)	10 (24)	10 (26)	1 (10)
Clorazepate	18 (2)	7 (3)	–	1 (4)	6 (7)	1 (1)	2 (2)	1 (2)	–	–
Diazepam	108 (15)	38 (14)	2 (5)	1 (4)	17 (19)	5 (5)	24 (21)	8 (19)	12 (31)	1 (10)
Flurazepam	96 (13)	39 (14)	4 (9)	2 (7)	12 (13)	10 (11)	18 (16)	3 (7)	8 (21)	–
Ketazolam	10 (1)	3 (1)	–	–	2 (2)	3 (3)	2 (2)	–	–	–
Lorazepam	139 (19)	43 (16)	7 (16)	5 (18)	17 (19)	13 (14)	23 (21)	13 (31)	13 (33)	5 (50)
Lormetazepam	94 (13)	36 (13)	2 (5)	1 (4)	12 (13)	12 (13)	15 (13)	9 (21)	6 (15)	1 (10)

Sch = schizophrenia, Psy = psychosis disorder, DelD = delusional disorder, SchAff = schizoaffective disorder, BPD = bipolar disorder, PDs = personality disorder, DepD = depresive disorders, ADD = anxiety-depresive disorder.

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Concomitant Treatments

Full treatments are shown as supplementary material (Table 5). Interestingly, antipsychotics are widely used not only in schizophrenia and psychosis (100% and 95%, respectively) but also in personality (66%), bipolar (61%) and schizoaffective (67%) disorders. In this regard, most of patients with schizophrenia were treated with at least 2 different antipsychotics (>67%). Furthermore, antidepressants were extensively used in depression (100%) and anxiety-depressive disorders (64%) but also in personality (49%). Finally, mood stabilizers were often used in bipolar and schizoaffective disorders (74% and 48% respectively).

Discussion

Anxiolytics and hypnotics have been one of the most prescribed drugs in Western countries. The 68% of patients in our cohort from mental health took benzodiazepines. The prevalence of benzodiazepine use in general population varies from 13.8% in France,[20] between 10 and 25% in the Netherlands,[21] and 26.1%in the United Kingdom.[22] First, our results demonstrated that the prescription of benzodiazepines was associated to women and to patients who use drugs of abuse. These results are in line with previous findings[23,24] suggesting that women could suffer more frequently affective health disorders or symptoms such as insomnia or anxiety. In addition, patients who use drugs may be not aware about the risks of benzodiazepines use. Second, while affective disorders are more likely prescribed with benzodiazepines, the use of LAIs are associated to a lower benzodiazepines intake and lower pharmacy costs.[17,25] Although several studies have already examined the influence of these factors either in the context of general population, primary care settings or in some particular mental disorders, the present study is, to the best of our knowledge, the first that investigates this issue using a cohort from mental health.

Diazepam Equivalents

Although our results demonstrated that to be woman is a risk factor to become prescribed with benzodiazepines, our data showed no differences in the dose of diazepam equivalents used by both women and men. This finding is consistent with previous reports using a cohort from mental health.[17] In this line, no differences between sexes were found in a cohort of patients diagnosed with schizophrenia.[26] In contrast, patients diagnosed with an affective disorder doubled the used dose of diazepam equivalents. Interestingly, patients treated with a LAI used

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lower diazepam equivalents. This finding was also found in patients diagnosed with psychotic disorders when oral versus LAIs antipsychotic treatments were compared.[26,27]

Use of Benzodiazepines by Sex and Mental Disorder

In both sexes, clonazepam and lorazepam were the more frequently prescribed benzodiazepines. Similarly, clonazepam and lorazepam were the most frequently prescribed in the different mental disorders. It worth to point out that clonazepam was more prevalent within non-affective disorders while lorazepam was more used in affective disorders. In this regard, clonazepam and lorazepam were also the most used benzodiazepines in several studies.[28,29] In contrast, other studies reported diazepam[30,31] or bromazepam[32] as the most used benzodiazepine. It is important to note that these divergences may occur due to the different groups studied and/or the several drugs that are available in different countries.

Overall, the present study demonstrated that the long-term (1-year) use of benzodiazepines is higher than desirable (>48%). In contrast, scientific evidence recommends the use of benzodiazepine as an adjuvant in treating anxiety, insomnia or depression only during the first four weeks of the treatment. As previously pointed out Smith and Tett,[33] clinical guidelines and restriction campaigns contribute to raise awareness of inappropriate use of benzodiazepines. Nonetheless, in Western countries, patients are not treated according to clinical guidelines based on scientific evidence.[23] It has been shown that long term use of benzodiazepines (>1 year) increased the risk of abstinence syndrome, accidents, suicide attempt (especially in depressed individuals), reduction of the work capability and increase in the costs of hospitalization.[20–22] Therefore, physicians should try to withdrawal benzodiazepines since the first prescription and try to avoid their use in the long-term management of the disease.

Limits

Given our inclusion/exclusion criteria were not restrictive; our cohort provides a high external validity to the western countries, in particular to Spain. Nonetheless, our study may hide some biases. For example, some clinical data, such as tobacco and drugs, are often unrecorded. Moreover, psychotropic medication could be also used in organic diseases such as neuropathic pain, migraine or others. Due to the lack about this information we could have overestimated the use of benzodiazepines in our cohort. In addition, Compliance with the LAIs was guaranteed given the treatment was administered by trained healthcare staff and it could impact

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in the need of concomitant treatments. Furthermore, considering that the severity of each patient's condition was not available from hospital records, it is not possible to elucidate whether patients of LAI groups had a worse prognosis versus patients treated with oral antipsychotics. Therefore, more studies including anxiety, anger, depression scales and prescriber habits are needed to truly establish the underlying reasons and risk factors involved in the prescription of benzodiazepines in mental health.

Conclusions

In summary, this is the first study showing the patterns of prescription of benzodiazepines in a cohort from mental health and comparing its dosage in diazepam equivalents. Despite the limitations of our study, we demonstrated that benzodiazepines are widely prescribed, mainly clonazepam followed by lorazepam and diazepam. Most of patients used at least one benzodiazepines and the daily mean intake of benzodiazepines corresponds to 25 mg of diazepam equivalents. Therefore, benzodiazepines are extensively prescribed and used at higher doses than desirable. Further research is needed to clarify the risk factors and reasons to benzodiazepine prescriptions; however, our findings could be useful for clinicians and their practice. ✤

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Conflict of Interests

None of the authors have conflict of interest.

Ethics Approval

Ethics and methodology issues approval for the study were granted by both the Research Ethic Committee of the Murcia Health Service and by the Ethic Committee of the San Antonio Catholic University of Murcia (UCAM) (CE031914). No identifiable information was retained or is presented in this manuscript.

Key points

1. Benzodiazepines are widely prescribed, mainly clonazepam followed by lorazepam and diazepam

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2. To be women and affective disorders are the main risk factors for the prescription of benzodiazepines while the long acting-injectables antipsychotics lower the risk.

References

1. Wick JY. The history of benzodiazepines. *Consult Pharm*. 2013;28(9):538–548. doi: 10.4140/TCP.n.2013.538.
2. Schallek W, Horst WD, Schlosser W. Mechanisms of action of benzodiazepines. *Adv Pharmacol Chemother*. 1979;16:45–87. doi: 10.1016/s1054-3589(08)60242–2.
3. Malcolm RJ. GABA systems, benzodiazepines, and substance dependence. *J Clin Psychiatry*. 2003; 64 Suppl 3:36–40.
4. Uzun S, Kozumplik O, Jakovljević M, Sedić B. Side effects of treatment with benzodiazepines. *Psychiatr Danub*. 2010;22(1):90–93.
5. Agencia Española de Medicamentos y Productos Sanitarios—Utilización de medicamentos ansiolíticos e hipnóticos en España durante el periodo 2000–2012. https://www.actasanitaria.com/wpcontent/uploads/2014/01/ansioliticos_hipnoticos-2000–2012.pdf
6. Paulose-Ram R, Jonas BS, Orwig D, Safran MA. Prescription psychotropic medication use among the U.S. adult population: results from the third national health and nutrition examination survey, 1988–1994. *J Clin Epidemiol*. 2004;57(3):309–317. doi: 10.1016/j.jclinepi.2003.05.001.
7. McIntosh B, Clark M, Spry C. Benzodiazepines in Older Adults: a review of clinical effectiveness, cost-effectiveness, and guidelines. Ottawa (ON): canadian agency for drugs and technologies in health; 2011 [cited 2020 Aug 14]. (CADTH Rapid Response Reports). Available from: http://www.ncbi.nlm.nih.gov/books/NBK174561/
8. Blanco C, Han B, Jones CM, Johnson K, Compton WM. Prevalence and Correlates of Benzodiazepine Use, Misuse, and Use Disorders Among Adults in the United States. *J Clin Psychiatry*. 2018;16:79 (6):18m12174. doi: 10.4088/JCP.18m12174.
9. Hollingworth SA, Siskind DJ. Anxiolytic, hypnotic and sedative medication use in Australia. *Pharmacoepidemiol Drug Saf*. 2010;19(3):280–288.
10. Lagnaoui R, Depont F, Fourrier A, Abouelfath A, Bégaud B, Verdoux H, et al. Patterns and correlates of benzodiazepine use in the French general population. *Eur J ClinPharmacol*. 2004;60(7):523–529.
11. Demyttenaere K, Bonnewyn A, Bruffaerts R, De Girolamo G, Gasquet I, Kovess V, Haro JM, Alonso J. Clinical factors influencing the prescription of antidepressants and benzodiazepines: results from the European study of the epidemiology of mental disorders (ESEMeD). *J Affect Disord*. 2008;110(1–2): 84–93. doi: 10.1016/j.jad.2008.01.011.
12. López-Pelayo H, Fàbrega-Ribera M, Garrido-Ocaña JM, Balcells-Oliveró MM, Gual-Solé A. Risk perception in the ongoing prescription of benzodiazepines in mental health and primary care. *Adicciones*. 2014;26(2):184–186.
13. Panes A, Fourrier-Réglat A, Verdoux H, Tournier M. Use and misuse of benzodiazepines in patients with psychiatric disorders. *Presse Med*. 2018;47(10):886–891. doi: 10.1016/j.lpm.2018.10.003
14. Clark RE, Xie H, Brunette MF. Benzodiazepine prescription practices and substance abuse in persons with severe mental illness. *J Clin Psychiatry*. 2004;65(2):151–155. doi: 10.4088/jcp.v65n0202.
15. Valenstein M, Taylor KK, Austin K, Kales HC, McCarthy JF, Blow FC. Benzodiazepine use among depressed patients treated in mental health settings. *Am J Psychiatry*. 2004;161(4):654–661. doi: 10.1176/appi.ajp.161.4.654.
16. Dong M, Zeng LN, Zhang Q, Yang SY, Chen LY, Najoan E, Kallivayalil RA, et al. Prescription of antipsychotic and concomitant medications for adult Asian schizophrenia patients: findings of the 2016 research on asian psychotropic prescription patterns (REAP) survey. *Asian J Psychiatr*. 2019;45:74–80. doi: 10.1016/j.ajp.2019.08.010.
17. García-Carmona JA, Simal-Aguado J, Campos-Navarro MP, Valdivia-Muñoz F, Galindo-Tovar A. Long acting-injectables antipsychotics: analysis of prescription patterns and patient's characteristics in mental health from a Spanish real-world study. *Clin Drug Inv*. 2020;40(5):459–468. doi: 10.1007/s40261-020-00913-7.
18. Elm E von, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *J Clin Epidemiol*. 2008;61:344–349. doi.10.1016/j.jclinepi.2007.11.008
19. Martínez-Andrés JA and García-Carmona JA. Clozapine, a controversial gold standard antipsychotic for the 21st century: switching to paliperidone palmitate 3-monthly improves the metabolic profile and lowers antipsychotic dose equivalents in a treatment-resistant schizophrenia cohort. *Schizophrenia Research*. 2019;212:234–236.

81-93_PB-Garcia-Carmona.indd 91 1/8/2021 11:36:03 AM

20. Bénard-Laribière A, Noize P, Pambrun E, Bazin F, Verdoux H, Tournier M, et al. Comorbidities and concurrent medications increasing the risk of adverse drug reactions: prevalence in French benzodiazepine users. *Eur J Clin Pharmacol*. 2016;72:869–876.
21. van Eijk JTM, Bosma H, Jonkers CCM, Lamers F, Muijrers PEM. Prescribing Antidepressants and benzodiazepines in the Netherlands: is chronic physical illness involved? *Depress Res Treat*. 2010. https://doi.org/10.1155/2010/10593 1.
22. Kapil V, Green JL, Le Lait C, Wood DM, Dargan PI. Misuse of benzodiazepines and Z-drugs in the UK. *Br J Psychiatr*. 2014;205:407–408.
23. Agarwal SA, Landon BE. Patterns in Outpatient Benzodiazepine Prescribing in the United States. *JAMA Netw Open*. 2019;2(1):e187399. doi: 10.1001/jamanetworkopen.2018.7399.
24. Olfson M, King M, Schoenbaum M. Benzodiazepine use in the United States. *JAMA Psychiatry*. 2015;72(2):136–142. doi: 10.1001/jamapsychiatry.2014.1763.
25. Pilon D, Tandon N, Lafeuille MH, Kamstra R, Emond B, Lefebvre P, Joshi K. Treatment Patterns, Health Care Resource Utilization, and Spending in Medicaid Beneficiaries Initiating Second-generation Long-acting Injectable Agents Versus Oral Atypical Antipsychotics. *Clin Ther*. 2017;39(10):1972.e2–1985.e2. doi: 10.1016/j.clinthera.2017.08.008.
26. Garcia-Carmona JA, Simal-Aguado J, Campos-Navarro P, Valdivia-Muñoz F, Galindo-Tovar A. Evaluation of long-acting injectable antipsychotics with the corresponding oral formulation in a cohort of patients with schizophrenia: a real-world study in Spain. *Int Clin Psychopharmacol*. 2021;1(36):18–24. doi: 10.1097/YIC.0000000000000339
27. Marić NP, Petrović SA, Jerotić S, Ristić I, Savić B, Zebić M, Vuković V, et al. Maintenance phase treatment of psychotic disorders in outpatients from Serbia—focus on long-term benzodiazepine use. *Int J Psychiatry Clin Pract*. 2020;24(3):315–321. doi: 10.1080/13651501.2020.1767788.
28. Comino-Naloto DC, Lopes CF, Barberato-Filho S, Cruz-Lopes L, Del Fiol FS, Bergamaschi C. Prescription of benzodiazepines for adults and older adults from a mental health clinic. *Cien Saude Colet*. 2016;21(4):1267–1276. doi: 10.1590/1413-81232015214.10292015.
29. Vicente-Sánchez MP, Macías-Saint-Gerons D, de la Fuente-Honrubia C, González-Bermejo D, Montero-Corominas D, Catalá-López F. Trends of use of anxiolytics and hypnotics in Spain from 2000 to 2011. *Rev Esp Salud Publica*. 2013;87(3):247–255. doi:10.4321/S1135727201300030004
30. Noia AS, Secoli SR, Duarte YAO, Lebrão ML, Lieber NSR. Fatores associados ao uso de psicotrópicos em idosos no município de São Paulo. *Rev Esc Enferm USP*. 2012;46:38–43.
31. Netto MUQ, Freitas O, Pereira LRL. Antidepressivos e benzodiazepínicos: estudo sobre o uso racional entre usuários do SUS em Ribeirão Preto. *Rev de Ciênc Farm Básica e Aplic*. 2012;33(1):77–81
32. Alvarenga JM, Loyola Filho AI, Firmo JO, Lima-Costa MF, Uchoa E. Prevalence and sociodemographic characteristics associated with benzodiazepines use among community dwelling older adults: the Bambuí health and aging study (BHAS). *Braz J Psychiatry*. 2008;30(1):7–11. doi: 10.1590/s1516-44462006005000062.
33. Smith AJ, Tett SE. Improving the use of benzodiazepines—is it possible? A non-systematic review of interventions tried in the last 20 years. *BMC Health Serv Res*. 2010;10:321. doi: 10.1186/1472-6963-10-321

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Supplementry Material

TABLE 5

Full Treatments by Mental Disorder

	TOTAL N = 735	SCH N = 277	PSY N = 44	DELD N = 28	SCHAFF N = 90	BPD N = 93	PDS N = 112	DEPD N = 42	ADD N = 39	OTHERS N = 10
N benzodiazepines (%)	**501 (68)**	**181 (65)**	**21 (48)**	**7 (25)**	**71 (79)**	**53 (57)**	**83 (74)**	**37 (88)**	**39 (100)**	**9 (90)**
1	338 (46)	126 (46)	17 (39)	5 (18)	48 (53)	34 (35)	50 (45)	27 (64)	22 (56)	9 (90)
2	141 (19)	46 (17)	4 (9)	2 (7)	18 (20)	18 (19)	27 (24)	9 (21)	17 (44)	–
3	21 (3)	9 (3)	–	–	4 (4)	1 (1)	6 (5)	1 (3)	–	–
N antipsychotics (%)	**535 (73)**	**277 (100)**	**42 (95)**	**14 (50)**	**61 (67)**	**57 (61)**	**74 (66)**	**5 (12)**	**2 (5)**	**3 (30)**
1	169 (23)	45 (16)	18 (41)	9 (32)	13 (14)	28 (30)	46 (41)	5 (12)	2 (5)	3 (30)
2	284 (39)	185 (67)	20 (45)	4 (14)	34 (38)	17 (18)	24 (21)	–	–	–
3	69 (9)	39 (14)	4 (9)	1 (4)	12 (13)	9 (9)	4 (3)	–	–	–
4	13 (2)	8 (3)	–	–	2 (2)	3 (3)	–	–	–	–
Biperiden (%)	**105 (14)**	**67 (24)**	**6 (14)**	**6 (21)**	**14 (16)**	**5 (5)**	**7 (6)**	–	–	-–
N antidepressants (%)	**250 (34)**	**64 (24)**	**10 (22)**	**7 (25)**	**22 (24)**	**21 (22)**	**55 (49)**	**42 (100)**	**25 (64)**	**4 (40)**
1	204 (28)	53 (19)	10 (22)	6 (21)	18 (20)	18 (19)	46 (41)	29 (69)	20 (51)	4 (40)
2	46 (6)	11 (4)	–	1 (4)	4 (4)	3 (3)	9 (8)	13 (31)	5 (13)	–
Mood stabilizer (%)	**200 (27)**	**39 (14)**	**5 (11)**	**4 (14)**	**43 (48)**	**69 (74)**	**27 (24)**	**8 (19)**	**4 (10)**	**1 (10)**
1	178 (24)	37 (13)	5 (11)	4 (14)	36 (40)	56 (60)	27 (24)	8 (19)	4 (10)	1 (10)
2	19 (3)	2 (1)	–	–	7 (8)	10 (11)	–	–	–	–
3	3 (0.4)	–	–	–	–	3 (3)	–	–	–	–

Sch = schizophrenia, Psy = psychosis disorder, DelD = delusional disorder, SchAff = schizoaffective disorder, BPD = bipolar disorder, PDs = personality disorder, DepD=depresive disorders, ADD = anxiety-depresive disorder.

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ORIGINAL RESEARCH ARTICLE

Long-Acting Injectable Antipsychotics: Analysis of Prescription Patterns and Patient Characteristics in Mental Health from a Spanish Real-World Study

Juan Antonio García-Carmona[1,2] · Jorge Simal-Aguado[3] · María Pilar Campos-Navarro[4] · Francisco Valdivia-Muñoz[5,6] · Alejandro Galindo-Tovar[3]

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Abstract

Background and Objective Long-acting injectable antipsychotics (LAIs) have been widely studied in schizophrenia and evidence suggests that they could be also used for the treatment of bipolar and schizoaffective disorders. Nonetheless, there are no studies evaluating their role in other psychiatric disorders. We aimed to evaluate the use of the newest monthly and 3-monthly LAIs—aripiprazole once monthly, paliperidone 1- and 3-monthly (PP1M, PP3M)—against the 2-weekly LAIs, using the following clinical outcomes: (1) the number of hospital re-admissions, (2) the number of documented suicidal behaviors/attempts, and (3) the use of concomitant treatments, including benzodiazepines, oral antipsychotics, and biperiden.

Methods A total of 431 patients were included who were treated with the corresponding LAI over at least 12 months and were previously diagnosed with a psychiatric disorder. Statistical analyses were performed using an ANCOVA model, Student's *t* test, and the Pearson's *r* test.

Results Our results showed significantly decreased re-admissions using PP3M versus the bi-weekly LAIs and aripiprazole once monthly, while no significant differences were found in suicidal behavior. Furthermore, we found a significantly lower intake of benzodiazepines in PP1M and PP3M groups versus the bi-weekly and aripiprazole once-monthly groups. In addition, patients treated with PP1M and PP3M used a significantly lower dose of haloperidol equivalents versus the bi-weekly LAIs group. Finally, significantly higher doses of biperiden were used by the bi-weekly LAIs group.

Conclusion In conclusion, paliperidone LAIs reduced hospital re-admissions and, as aripiprazole once monthly, lowered concomitant psychiatric medication versus the bi-weekly LAIs. Further research and analysis of subgroups are needed; however, these findings might be useful for clinicians.

1 Introduction

In Spain, the estimated prevalence of schizophrenia and related disorders is 3–6/1000 inhabitants [1, 2], for bipolar disorder it is 2.5–3.4/1000 inhabitants [3], and for personality disorders about 1.5–1.7/1000 inhabitants [4, 5]. Antipsychotics are the main treatment for psychotic symptoms, which typically appear in patients suffering from psychosis, schizophrenia, schizoaffective, and delusional disorders, but also may appear in patients with bipolar and personality diorders [6]. In order to improve adherence to treatment, antipsychotics were formulated first as depot and later as long-acting injectables (LAIs). Fluphenazine and zuclopentixol are classified as first-generation antipsychotics; they were developed in the 1960s and both are available as bi-weekly formulations [7, 8]. In the 2000s, a second generation of LAI antipsychotics

✉ Juan Antonio García-Carmona
dr.jagarcar@gmail.com

1 Service of Neurology, Santa Lucía University Hospital, C/ Mezquita s/n, 30202 Cartagena, Murcia, Spain

2 Unit of Acute Psychiatry, Reina Sofía University Hospital, Murcia, Spain

3 Department of Pharmacy, Health Sciences Faculty, San Antonio Catholic University of Murcia, UCAM, Murcia, Spain

4 Unit of Acute Psychiatry, Santa Lucia University Hospital, Cartagena, Murcia, Spain

5 Center of Mental Health Infante, Murcia, Spain

6 Center of Mental Health Cartagena, Cartagena, Murcia, Spain

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Key Points

Aripiprazole and paliperidone LAIs reduced hospital admission compared with the bi-weekly LAIs.

Paliperidone LAIs were associated with lower intake of concomitant benzodiazepines and antipsychotics.

Only about a 14% of LAIs were used as monotherapy while more than 40% of patients used at least one benzodiazepine and one antipsychotic.

emerged. Risperidone and olanzapine became available in 2003 and 2008, respectively, and were typically administered as bi-weekly formulations [9, 10]. Despite being considered second-generation LAIs, aripiprazole and paliperidone (PP1M) LAIs emerged as monthly formulations in 2013 and 2009, respectively [11, 12]. Paliperidone has also been available as a 3-monthly (PP3M) formulation since 2015 [13].

LAIs have been widely studied in schizophrenia, and have shown an increased adherence to treatment and prevention of relapses [14, 15]. More recent evidence suggests that antipsychotics and LAIs could be used not only for schizophrenia but also for the treatment and maintenance of bipolar disorder and schizoaffective disorders [16, 17]. Despite antipsychotics being used for the treatment of personality disorders, there are limited reports for the use of paliperidone or risperidone LAIs [18, 19]. Recently it has been demonstrated that LAIs reduced suicide risk and suicidal behavior in schizophrenia [20]; however, there are no studies evaluating their role in other psychiatric disorders. Although there are several studies comparing different clinical outcomes between LAIs and their corresponding oral formulations, as well as between first- and second-generation LAIs, there are limited studies comparing monthly with bi-weekly LAIs showing similar adherence to treatment [21, 22].

Here, we present results from a cohort of patients from the Region of Murcia, Spain. We aimed to evaluate the use of the newest monthly and 3-monthly LAIs—aripiprazole once monthly, PP1M, and PP3M—versus the bi-weekly LAIs fluphenazine, zuclopentixol, risperidone, and olanzapine, using the following clinical outcomes: (1) the number of hospital re-admissions, (2) the number of documented suicidal behaviors/attempts, and (3) the use of concomitant treatments, including benzodiazepines, oral antipsychotics, and biperiden.

2 Methods

2.1 Study Design

We designed a cross-sectional study, from 2015 to 2017, based on a representative sample of the adult and non-institutionalized general population of the Murcia region. A total of 1478,509 habitants were living at Region of Murcia (2017), half of them in the two main cities, Murcia and Cartagena. The cohort of patients was collected through electronic records (Selene, Siemens, Germany) from the main mental health centers in Murcia (Reina Sofía University Hospital, CSM Infante, and CSM Murcia-Este) and Cartagena (Santa Lucía University Hospital and CSM Cartagena). These centers, serving a population of 505,910, are located at health areas 2 and 7 of the Region of Murcia, corresponding to Murcia-Este and Cartagena.

A total number of 431 patients who met the following inclusion criteria were included: they were $\geq$ 18 years old, they were treated with the corresponding LAI for at least 12 months, no other LAI was administered, and they were previously diagnosed with schizophrenia, psychosis, or schizoaffective, delusional, bipolar, or personality disorders according to the Diagnostic and Statistical Manual of Mental Disorders (DSM)-5 guidelines. Exclusion criteria included institutionalized patients, use of two LAIs, intellectual disability or autistic spectrum disorder, and patients with missing records or unable to confirm treatment continuation for 1 year. The present study was drawn up following the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) statement items [23].

2.2 Study Measures

Data collected include demographical information such as age, sex, civil status, tobacco and other drug use, as well as clinical data such as the type of disorder, its evolution (years) and the LAI dosage (Table 1). Furthermore, we collected the number of hospital admissions and documented suicidal behaviors/attempts and use of concomitant psychiatric medications, including other antipsychotics, benzodiazepines, and biperiden.

Moreover, the number of hospital admissions and the documented suicidal behaviors/attempts were collected during treatment with the LAI (for at least 1 year) and expressed as the corresponding percentage/year. The treatments were compared by calculating the daily dose of biperiden and the daily equivalent dose of antipsychotics and benzodiazepines by using haloperidol or diazepam as standards to compare the corresponding doses as previously published by the authors [24] using tables of equivalences [25–27].

Table 1 Demographic and clinical variables

Variable	Global ($n = 431$)	Aripiprazole once monthly ($n = 139$)	PP1M ($n = 162$)	PP3M ($n = 95$)	2w-LAIs ($n = 35$)	p value
Sex, *n* (%)						**0.001**
Women	159 (36.9)	70 (50.4)	46 (28.4)	32 (34.7)	11 (31.4)	
Men	272 (63.1)	69 (49.6)	116 (71.6)	63 (65.3)	24 (68.6)	
Age, y (mean ± SEM)	41.81 ± 0.55	39.98 ± 0.96	42.71 ± 0.91	42.09 ± 1.17	44.18 ± 1.83	0.104
Civil status, *n* (%)						0.163
Single/divorced	351 (81.5)	107 (77.0)	132 (81.5)	80 (84.2)	32 (91.4)	
Couple/married	80 (18.5)	32 (23.0)	30 (18.5)	15 (15.8)	3 (8.6)	
Illness evolution, y (± SEM)	13.4 (0.5)	11.6 (0.8)	13.8 (0.8)	14.2 (1.1)	16.77 (1.5)	**0.023**
Mental disorder, *n* (%)						
Personality	48 (11.1)	18 (12.9)	16 (9.9)	11 (11.6)	3 (8.6)	
Bipolar	52 (12.1)	29 (20.9)	15 (9.3)	3 (3.2)	5 (14.3)	
Schizoaffective	60 (13.9)	25 (18.0)	19 (11.7)	10 (10.5)	6 (17.1)	
Psychosis	37 (8.6)	9 (6.5)	16 (9.9)	10 (10.5)	2 (5.7)	
Schizophrenia	209 (48.5)	51 (36.7)	87 (53.7)	53 (55.8)	18 (51.4)	
Delusional	25 (5.8)	7 (5.0)	9 (5.6)	8 (9.4)	1 (2.9)	
Drug use, *n* (%)						0.105
Tobacco	88 (20.4)	26 (18.7)	40 (24.7)	13 (13.7)	9 (25.7)	
Other drugs	25 (5.8)	9 (6.5)	7 (4.3)	9 (9.5)	–	

Significant p values are given in bold

LAI long-acting injectable, *PP1M* paliperidone palmitate once monthly LAI, *PP3M* paliperidone palmitate 3-monthly LAI, *2w-LAIs* bi-weekly LAIs including risperidone, olanzapine, zuclopenthixol, and fluphenazine, *y* years

2.3 Statistical Analysis and Confounding Factors

All values are expressed as the mean ± SEM. All statistical analyses were performed using SPSS statistics v. 20 (IBM, Armonk, NY, USA). ANOVA or the Chi^2-test was used for the comparison of baseline characteristics between the different groups. The following variables were found to be adjusted by group of LAI: sex and years of disease duration. Pearson's r test was used for correlation analysis between the dependent variables and age. Student's t test was used to compare the dependent variables between men and women. To assess differences among the LAI groups, an analysis of covariance (ANCOVA) model was used followed by the Bonferroni post hoc test with LAI and the psychiatric disorder as fixed factors and sex and illness disease duration as covariates. Differences with a p value < 0.05 were considered significant.

3 Results

A total of 431 patients using a LAI for a minimum duration of 1 year were identified. These patients used the following doses: aripiprazole once monthly: 395.7 mg/month, $n = 139$ (32.3%); PP1M: 153.8 mg/month, $n = 162$ (37.6%); PP3M: 458.7 mg/3 months, $n = 95$ (22.0%) and 35 (8.1%) corresponding to the bi-weekly LAIs group (risperidone: 93.75 mg/bi-weekly, $n = 18$; zuclopentixol: 193.8 mg/bi-weekly, $n = 13$; olanzapine: 255 mg/bi-weekly, $n = 2$; fluphenazine: 25 mg/bi-weekly, $n = 2$). Sample characteristics are shown in Table 1. The Chi^2 test showed a significant effect of sex ($p = 0.001$) for the use of LAIs. Specifically, all LAIs were more frequently used in men with the exception of aripiprazole once monthly, which was used in a similar manner in both men and women. No significant differences were observed in the age, civil status, and use of drugs between groups. Nonetheless, a one-way ANOVA showed a significant difference ($p = 0.023$) in the years of disease evolution, with the longest being in the bi-weekly LAIs group.

3.1 Hospital Re-admissions

The number of hospital re-admissions were assessed and expressed as the percentage per group for the period from 2015 to 2017. The mean for the cohort was 8.28% (8.28 ± 0.7). Pearson's r test showed a significant negative correlation between the age and the number of hospital re-admissions ($r = -0.1062$, $p = 0.033$; Fig. 1a). No sex differences were found in re-admissions (Student's t test: $t_{[df=1430]} = 0.163$; $p = 0.8706$; Fig. 1b). The ANCOVA model did not demonstrate any statistical differences ($p = 0.0686$) for re-admissions between the included psychiatric disorders

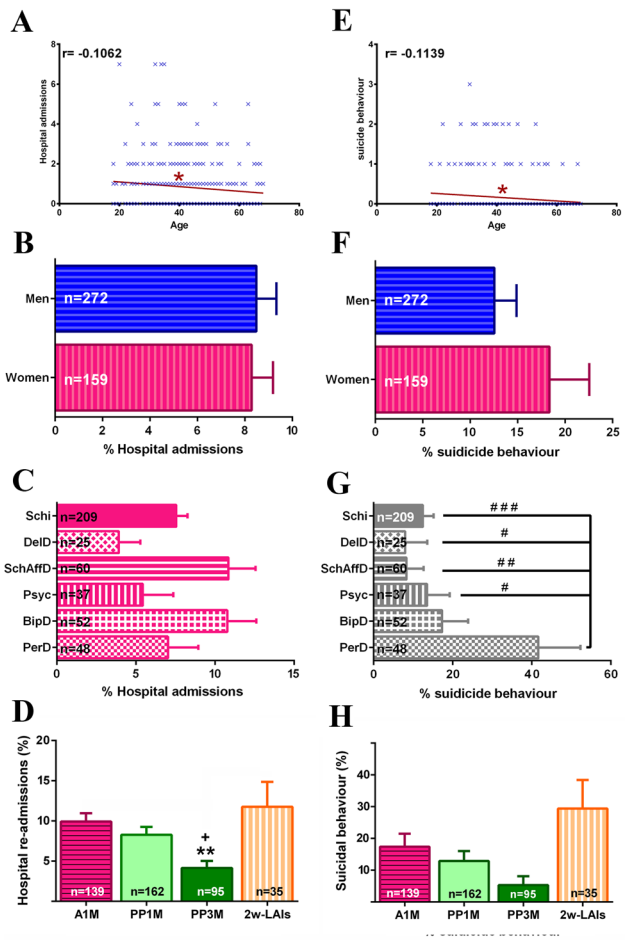

Fig. 1 Hospital readmissions and suicidal behavior. Correlation between age and hospital readmissions (**a**) and suicidal behavior (**e**) (Pearson's *r* test; $*p < 0.05$, significant negative correlation). Hospital readmissions (%) and suicidal behavior (%) by sex (**b**, **f**; Student's *t* test); mental disorders (**c**, **g**; ANCOVA model) and long-acting injectables (LAIs) (**d**, **h**; ANCOVA model). Data are expressed as mean ± SEM. $^{\#}p < 0.05$, $^{\#\#}p < 0.01$, $^{\#\#\#}p < 0.001$ vs. PersD; $**p < 0.01$ vs. A1M; $^{+}p < 0.05$ vs. 2W-LAIs. *Schi* schizophrenia, *DelD* delusional disorder, *SchAffD* schizoaffective disorder, *Psyc* psychosis, *BipD* bipolar disorder, *PerD* personality disorder, *A1M* aripiprazole once monthly, *PP1M* paliperidone palmitate once monthly, *PP3M* paliperidone palmitate 3-monthly, *2w-LAIs* bi-weekly LAIs

(Fig. 1c). In contrast, ANCOVA analysis revealed a significant difference ($p = 0.002$) between the different LAIs and re-admissions (Fig. 1d). The Bonferroni post hoc test showed a significant decrease in re-admissions using PP3M (4.17 ± 1.25) versus the bi-weekly LAIs (11.35 ± 2.07; $p = 0.018$) and aripiprazole once monthly (9.71 ± 1.06; $p = 0.005$).

3.2 Suicidal Behavior/Attempts

The number of suicidal behaviors or attempts was expressed as the percentage/year for the period from 2015 to 2017; 14.7% (14.7 ± 2.4) of the patients in this cohort showed suicidal behavior. As shown in Fig. 1e, there was a significant negative correlation between age and the number of suicidal behaviors/attempts ($r = -0.1062$, $p = 0.033$). No significant sex differences were observed ($t_{[df=1430]} = 1.313$; $p = 0.1899$; Fig. 1f). Nonetheless, the ANCOVA model showed significant differences ($p = 0.0013$) for suicidal behavior between the different psychiatric disorders included in the current study (Fig. 1g). In particular, the Bonferroni post hoc test showed that personality disorder patients (41.7 ± 10.7) have higher suicidal attempts than schizophrenia (12.4 ± 2.7; $p = 0.0006$), schizoaffective (8.3 ± 4.3; $p = 0.0015$), delusional (8.0 ± 5.5; $p = 0.0269$) and psychotic (13.5 ± 6.6; $p = 0.0435$) disorder patients. As shown in Fig. 1h, the ANCOVA showed no significant differences ($p = 0.130$) between the different LAIs with regard to suicidal behavior.

3.3 Concomitant Treatments

The number of patients in which LAIs were used as monotherapy as well as the numbers of cases in which benzodiazepines, antipsychotics, and biperiden were used concomitantly is shown in Table 2. The use of LAIs as a monotherapy was approximately 14%, with higher rates among both PP1M and PP3M, while more than half of the patients used benzodiazepines and antipsychotics. Figure 2 summarizes the data from the main concomitant oral medication in our cohort, with mean daily doses (mg/day) of: benzodiazepines 18.223 ± 1.571, antipsychotics 4.053 ± 0.390, and biperiden 0.591 ± 0.081. As shown in Fig. 2a, e, i, no significant correlation was found between age and the use of benzodiazepines ($r = -0.01181$), antipsychotics ($r = -0.03948$), or biperiden ($r = -0.04805$). Furthermore, no significant differences were found between men and women for diazepam equivalents (Fig. 2b; $t_{[df=1430]} = 0.6053$; $p = 0.5453$), haloperidol equivalents (Fig. 2f; $t_{[df=1430]} = 0.8016$; $p = 0.4236$), and biperiden (Fig. 2j; $t_{[df=1430]} = 0.1268$; $p = 0.8992$). Furthermore, ANCOVA failed to show statistical differences for the use of benzodiazepine equivalents ($p = 0.1527$), antipsychotic equivalents ($p = 0.1503$), and biperiden ($p = 0.3302$) between the disorders in our cohort. As shown in Fig. 2d, h, l, the ANCOVA model showed significant differences between the LAIs regarding the intake of diazepam ($p = 0.0001$) and haloperidol ($p = 0.011$) equivalents as well as biperiden ($p = 0.002$). Specifically, the Bonferroni post hoc test demonstrated that lower benzodiazepine intake is associated with the paliperidone PP1M (12.565 ± 2.167; $p = 0.0001$) and PP3M (7.879 ± 2.820; $p = 0.0001$) versus bi-weekly LAIs (37.197 ± 4.653) and aripiprazole once monthly (26.053 ± 2.379) groups. In addition, patients treated with PP1M (3.193 ± 0.540; $p = 0.023$) and PP3M (3.107 ± 0.701; $p = 0.031$) used significantly lower doses of haloperidol equivalents versus the patients treated with

Table 2 Dosage and concomitant treatments

Treatment	Global ($n=431$)	Aripiprazole once monthly ($n=139$)	PP1M ($n=162$)	PP3M ($n=95$)	2w-LAIs ($n=35$)
LAI dose, mg/month (±SEM)		395.7 (±5.4)	153.8 (±5.8)	458.7 (±20.7)[φ]	[φ]
LAIs in monotherapy (%)	63 (14.6)	10 (7.2)	24 (14.8)	25 (26.3)	4 (11.4)
Benzodiazepines, *n* (%)	256 (59.4)	96 (69.1)	94 (58.0)	39 (41.1)	27 (77.1)
1	177 (41.1)	59 (42.4)	70 (43.2)	31 (32.6)	17 (48.6)
2	67 (15.5)	31 (22.3)	22 (13.6)	8 (8.5)	6 (17.1)
3	11 (2.6)	6 (4.4)	2 (1.2)	–	3 (8.6)
4	1 (0.2)	–	–	–	1 (2.8)
Antipsychotics, *n* (%)	238 (55.2)	77 (55.4)	86 (53.1)	48 (50.5)	27 (77.1)
1	177 (41.1)	57 (41.0)	67 (41.4)	38 (40.0)	15 (42.9)
2	55 (12.8)	19 (13.7)	18 (11.1)	7 (7.4)	11 (31.4)
3	5 (1.2)	–	1 (0.6)	3 (3.1)	1 (2.8)
4	1 (0.2)	1 (0.7)	–	–	–
Biperiden, *n* (%)	65 (15.1)	13 (9.4)	28 (17.3)	13 (13.7)	11 (31.4)

PP1M paliperidone palmitate once monthly LAI, *PP3M* paliperidone palmitate 3-monthly LAI, *2w-LAIs* bi-weekly LAIs including risperidone, olanzapine, zuclopenthixol, and fluphenazine, *y* years

[φ]3-monthly dose for PP3M and see *Results* section for mean doses of specific bi-weekly LAIs

the bi-weekly LAIs (6.90 ± 1.156). Finally, post hoc tests showed significantly increased doses of biperiden with the use of the bi-weekly LAIs (1.456 ± 0.240) versus PP1M (0.628 ± 0.112; $p=0.011$), PP3M (0.551 ± 0.146; $p=0.008$), and aripiprazole once monthly (0.410 ± 0.123; $p=0.001$).

4 Discussion

Most of our patients, both men and women, were single or divorced, suggesting that suffering a mental disorder may result in social impairment, as previously shown [28]. The prevalence of tobacco smokers and drug users in our cohort was 20.4% and 5.8%, respectively, similar to the prevalence of the general population in Spain in 2017 (22.7% and 5.8%) [29]. Our findings are in contrast with previous studies showing increased prevalence of tobacco and illicit drug use among patients with schizophrenia [30, 31], which could be due to unrecorded data from patients and including different disorders.

Focusing on the LAIs, we found that aripiprazole once monthly was distributed equally between the sexes while the other LAIs were more widely used in men. One explanation could be that paliperidone is used for the management of hostility among patients with schizophrenia and related mental disorders [32], a symptom/condition that is more common in men, while no data have been shown with aripiprazole once monthly in the long-term for the management of aggressiveness [33]. Another hypothesis could be the use of aripiprazole once monthly in women to avoid side effects reported more frequently with other antipsychotics, such as weight gain [34], increased prolactin levels, and amenorrhea [35] or extrapyramidal effects [36].

4.1 Hospital Re-Admissions

We found no sex differences in hospital re-admissions; however, younger patients experienced more hospital re-admissions. Although not statistically significant, there is a strong trend for higher re-admissions in schizoaffective and bipolar disorders. Our results also showed that patients treated with PP3M experienced less re-admissions versus aripiprazole once monthly and the bi-weekly LAIs.

Different studies have shown that LAIs reduced re-admissions versus oral formulations in schizophrenia, schizoaffective, and bipolar disorders [37]. Some studies compared different LAIs showing controversial results. A recent study showed no difference in time to re-admission between the second- and first-generation antipsychotic LAIs in patients with schizophrenia and schizoaffective disorders. Nonetheless, this study used a post hoc analysis suggesting that PP1M and aripiprazole once monthly LAIs may have a more favorable profile in terms of time to re-admission compared with risperidone and olanzapine bi-weekly LAIs [38]. Another study showed that there was no association with increased admissions 3 years post-treatment with PP1M or other LAIs including aripiprazole once monthly and bi-weekly LAIs [39]. Although some studies have been published comparing re-admissions between different LAIs, this is the first that includes a group of patients treated with PP3M. Since clinical data about the severity of the condition were not available for these patients, it is possible that our

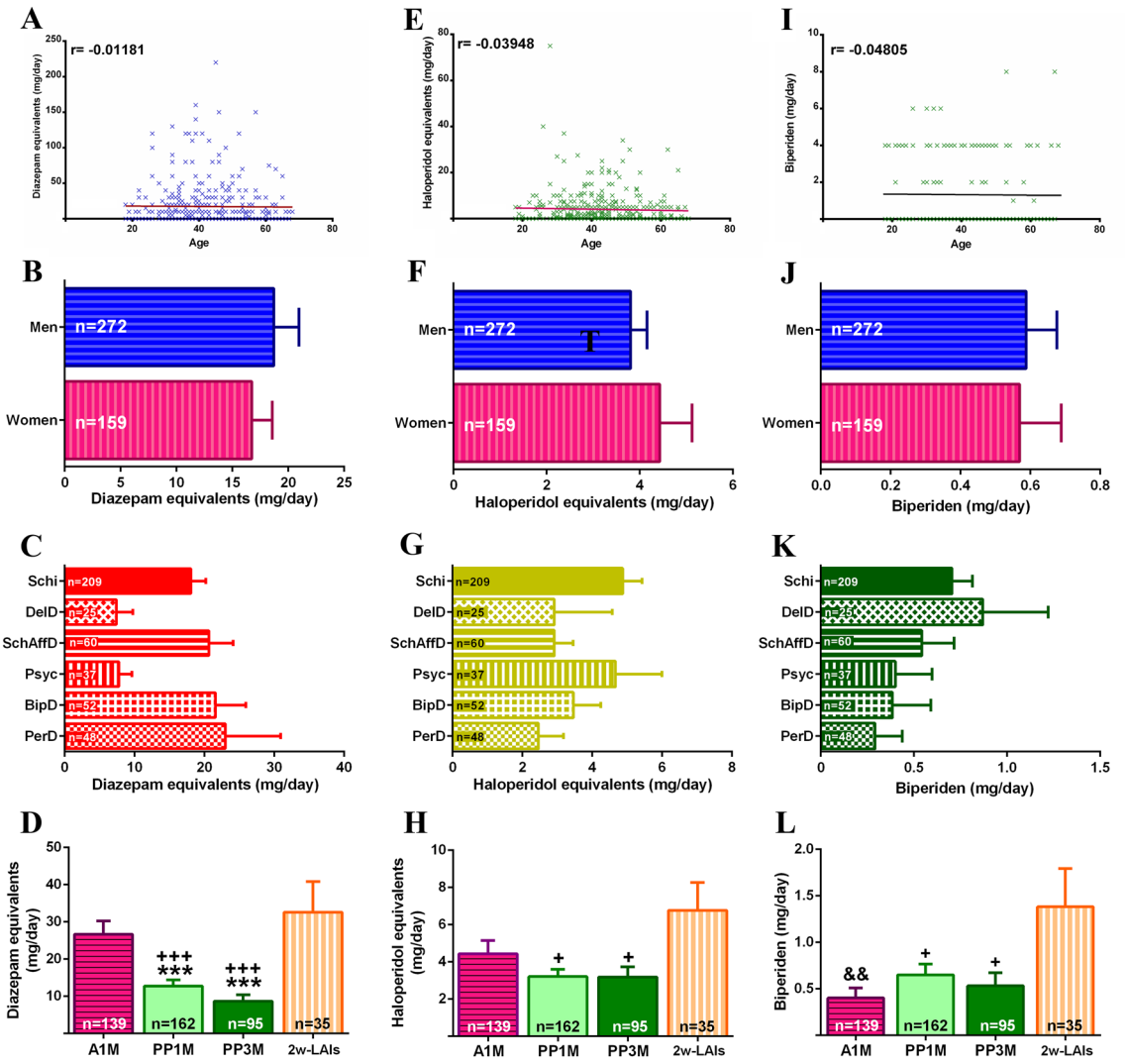

Fig. 2 Psychiatric concomitant treatments. Correlation between age and dose (mg/day) of diazepam (**a**) and haloperidol (**e**) equivalents and biperiden (**i**) (Pearson's *r* test; not significant). Dose of benzodiazepines showed as diazepam and haloperidol equivalents and biperiden by sex (**b**, **f**, **j**; Student's test), mental disorders (**c**, **g**, **k**; ANCOVA model) and by long-acting injectable (LAI) group (**d**, **h**, **l**; ANCOVA model). Data are expressed as mean ± SEM. $^{***}p < 0.001$ vs. A1M, $^{+}p < 0.05$, $^{+++}p < 0.001$ vs. 2w-LAIs; $^{\&\&}p < 0.01$ vs. 2w-LAIs. *Schi* schizophrenia, *DelD* delusional disorder, *SchAffD* schizoaffective disorder, *Psyc* psychosis, *BipD* bipolar disorder, *PerD* personality disorder, *A1M* aripiprazole once monthly, *PP1M* paliperidone palmitate once monthly, *PP3M* paliperidone palmitate 3-monthly, *2w-LAIs* bi-weekly LAIs

results are due to the fact that PP3M is usually administered following clinical stabilization with the monthly formulation and, therefore, is used in the less symptomatic phases of the disease. Further research is needed to clarify this finding.

4.2 Suicidal Behavior

Similar to hospital re-admissions, our results showed increased suicidal behavior among younger patients and was more frequent in patients diagnosed with personality disorder (around 40%/year). No sex differences were observed. Our results are in line with previous reports suggesting that younger patients showed increased suicidal behavior in schizophrenia [40], affective disorders [41], and personality disorders [42]. This finding may be explained by the lower access to mental health services and to the emotional impairment of the diagnosis among young people [43]. Nonetheless, there is limited research evaluating the role of LAIs in suicide. While we observed no significant differences between LAIs, our results showed that bi-weekly LAIs might be associated with worse control of suicidal behavior. In this regard, some studies showed that second-generation LAIs reduced suicidal behavior and ideation in schizophrenia [44, 45]. To the best of our knowledge this is the first study

comparing the different LAIs in suicidal behavior. However, further studies are needed to assess this issue.

4.3 Pharmacological Treatments

No differences were shown for the use of concomitant psychiatric treatments by age, sex, or psychiatric disorder. It is worth noting that, while we observed no statistically significant differences, patients with affective and personality disorders used more benzodiazepines and patients with psychotic-related disorders used more antipsychotics and biperiden. Focusing on the LAIs groups, we found that both PP1M and PP3M lowered benzodiazepine use versus the aripiprazole once monthly and bi-weekly groups. While antipsychotics are superior to benzodiazepines for the treatment of psychotic symptoms, a recent systematic review showed that benzodiazepines as adjunct therapy to antipsychotics are superior to antipsychotics for the treatment of schizophrenia [46]. On the other hand, benzodiazepines are generally prescribed to achieve sedation or to manage aggressive behavior in patients with psychosis [47]. Our findings can be explained by the fact that paliperidone has higher efficacy (although not significant) in managing psychotic symptoms as well as aggressive behavior compared to aripiprazole and bi-weekly LAIs [48, 49]. Another reason could be that aripiprazole is known to cause akathisia [50] more frequently compared with other antipsychotics, which could be managed using benzodiazepines [51].

In addition, monthly and 3-monthly LAIs lowered concomitant antipsychotics versus the bi-weekly group. Our results are in contrast with previous data showing that second-generation antipsychotic LAIs were associated with increased use of oral antipsychotics [52]. This discrepancy may originate from differences in the treatments since risperidone was the most prevalent LAI in the second-generation antipsychotic LAI group in the aforementioned study, while in our study it was included in the bi-weekly group. Nonetheless, our results are in line with a previous study showing that PP1M was associated with lower use of concomitant oral antipsychotics (58.8%) versus risperidone (88.9%) and fluphenazine LAIs (80%) [53]. Similarly, Aggarwal et al. showed no differences regarding the use of concomitant oral antipsychotics when comparing the bi-weekly LAIs risperidone, fluphenazine, or haloperidol [54]. It is possible that the decreased use of oral antipsychotics with PP1/3M is due to greater knowledge or confidence of clinicians with this LAI. Another explanation could be that patients are initially prescribed oral medications, and clinicians could be hesitant to compromise the patient's stability by making changes to a long-term medication regimen.

Finally, monthly and 3-monthly LAIs were associated with lower biperiden intake compared with the bi-weekly LAIs. The use of biperiden is closely related to the prevention of extrapyramidal effects. Our research is in line with previous data showing no sex differences in the prevalence of extrapyramidal side effects [55]. In contrast with our results, a recent meta-analysis showed no association between extrapyramidal side effects and class or specific antipsychotic, and another study showed no differences between first- and second-generation antipsychotics [55, 56]. Therefore, our results could be due to the higher polypharmacy in the bi-weekly group, as suggested in a recent systematic review [57].

5 Limitations

Given that our inclusion/exclusion criteria were not restrictive, our cohort could provide high external validity to Western countries, in particular Spain. Nonetheless, on the one hand, the use of the LAIs was found to differ between men and women and also among patients with longer disease evolution. We included these variables as covariates to avoid bias effects. However, our study may have less apparent biases. For example, some clinical data, such as use of tobacco and drugs, are often un-recorded. Therefore, the prevalence of smokers and drug users could be underestimated in our cohort. Furthermore, considering that the severity of each patient's condition was not available from hospital records, it is possible that patients treated with 3-monthly LAIs had a better prognosis or required less frequent follow-up assessments compared with patients treated with monthly and bi-weekly LAIs. Moreover, although hospital re-admissions are a useful marker of effectiveness, they are also more easily affected by other variables, such as patient's social and family support, which are unrelated to the LAI medication. Finally, given that most research has been carried out in schizophrenia, a subgroup analysis will be necessary to better show the role of the different LAIs in mental health.

6 Conclusions

To the best of our knowledge, this is the first study to compare the use of concomitant psychiatric drugs and suicidal behavior between different LAIs. Despite the limitations of our study, we demonstrated that paliperidone LAIs reduced hospital re-admissions and, as aripiprazole once monthly, lowered concomitant psychiatric medication versus the bi-weekly LAIs in mental health. Further research and analysis of subgroups is needed to clarify the effects and interactions of LAIs, however, but our findings could be useful for clinicians and their practice.

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Compliance with Ethical Standards

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References

1. Moreno-Küstner B, Mayoral F, Navas-Campaña D, García-Herrera JM, Angona P, Martín C, Rivas F. Prevalence of schizophrenia and related disorders in Malaga (Spain): results using multiple clinical databases. Epidemiol Psychiatr Sci. 2016;25(1):38–48. https://doi.org/10.1017/S2045796014000614.
2. Ayuso-Mateos JL, Gutierrez-Recacha P, Haro JM, Chisholm D. Estimating the prevalence of schizophrenia in Spain using a disease model. Schizophr Res. 2006;86(1):194–201. https://doi.org/10.1016/j.schres.2006.06.003.
3. Calvó-Perxas L, Garre-Olmo J, Vilalta-Franch J. Prevalence and sociodemographic correlates of depressive and bipolar disorders in Catalonia (Spain) using DSM-5 criteria. J Affect Disord. 2015;184:97–103. https://doi.org/10.1016/j.jad.2015.05.048.
4. Bobes J, Iglesias-García C, García-Portilla González MP, Bascarán MT, Jiménez-Treviño L, Pelayo-Terán JM, Rodríguez-Revuelta J, Sánchez-Lasheras F, Sáiz-Martínez P. Changes in administrative prevalence of mental disorders over a 13-year period in Asturias (northern Spain). Rev Psiquiatr Salud Ment. 2013;6:60–6. https://doi.org/10.1016/j.rpsmen.2012.10.002.
5. Aragonés E, Salvador-Carulla L, López-Muntaner J, Ferrer M, Piñol JL. Registered prevalence of borderline personality disorder in primary care databases. Gac Sanit. 2013;27(2):171–4. https://doi.org/10.1016/j.gaceta.2011.12.006.
6. Gaebel W, Zielasek J. Focus on psychosis. Dialogues Clin Neurosci. 2015;17:9–18.
7. Maayan N, Quraishi SN, David A, Jayaswal A, Eisenbruch M, Rathbone J, Asher R, Adams CE. Fluphenazine decanoate (depot) and enanthate for schizophrenia. Cochrane Database Syst Rev. 2015;2:CD000307. https://doi.org/10.1002/14651858.cd000307.pub2.
8. Coutinho E, Fenton M, Quraishi S. Zuclopenthixol decanoate for schizophrenia and other serious mental illnesses. Cochrane Database Syst Rev. 2000;(2):CD001164.
9. Heres S, Kraemer S, Bergstrom RF, Detke H. Pharmacokinetics of olanzapine long-acting injection: the clinical perspective. Int Clin Psychopharmacol. 2014;29(6):299–312. https://doi.org/10.1097/YIC.0000000000000040.
10. Rainer M. Risperidone long-acting injection: a review of its long term safety and efficacy. Neuropsychiatr Dis Treat. 2008;4(5):919–27.
11. Raoufinia A, Peters-Strickland T, Nylander AG, Baker R, Eramo A, Jin N, Bricmont P, Repella J, McQuade R, Hertel P, Larsen F. Aripiprazole once-monthly 400 mg: comparison of pharmacokinetics, tolerability, and safety of deltoid versus gluteal administration. Int J Neuropsychopharmacol. 2017;1(20):295–304. https://doi.org/10.1093/ijnp/pyw116.
12. Morris M, Tarpada S. Long-acting injectable paliperidone palmitate: a review of efficacy and safety. Psychopharmacol Bull. 2017;47(2):42–52.
13. Savitz A, Xu H, Gopal S, Nuamah I, Ravenstijn P, Janik A, Schotte A, Hough D, Fleischhacker W. Efficacy and safety of paliperidone palmitate 3-month formulation for patients with schizophrenia: a randomized, multicenter, double-blind, noninferiority study. Int J Neuropsychopharmacol. 2016. https://doi.org/10.1093/ijnp/pyw018.
14. Stip E, Lachaine J. Real-world effectiveness of long-acting antipsychotic treatments in a nationwide cohort of 3957 patients with schizophrenia, schizoaffective disorder and other diagnoses in Quebec. Ther Adv Psychopharmacol. 2018;8(11):287–301. https://doi.org/10.1177/2045125318782694.
15. Tiihonen J, Mittendorfer-Rutz E, Majak M, et al. Real-world effectiveness of antipsychotic treatments in a nationwide cohort of 29 823 patients with schizophrenia. JAMA Psychiatry. 2017;74:686–93.
16. Cipriani A, Barbui C, Salanti G, Rendell J, Brown R, Stockton S, Purgato M, Spineli LM, Goodwin GM, Geddes JR. Comparative efficacy and acceptability of antimanic drugs in acute mania: a multiple-treatments meta-analysis. Lancet. 2011;378:1306–15. https://doi.org/10.1016/S0140-6736(11)60873-8.
17. Llorca P, Abbar M, Courtet P, Guillaume S, Lancrenon S, Samalin L. Guidelines for the use and management of long-acting injectable antipsychotics in serious mental illness. BMC Psychiatry. 2013;13:340–57.
18. Palomares N, Montes A, Díaz-Marsá M, Carrasco JL. Effectiveness of long-acting paliperidone palmitate in borderline personality disorder. Int Clin Psychopharmacol. 2015;30(6):338–41. https://doi.org/10.1097/YIC.0000000000000095.
19. Carrasco JL, Palomares N, Marsá MD. Effectiveness and tolerability of long-acting intramuscular risperidone as adjuvant treatment in refractory borderline personality disorder. Psychopharmacology. 2012;224(2):347–8. https://doi.org/10.1007/s00213-012-2880-0.
20. Corigliano V, Comparelli A, Mancinelli I, Montalbani B, Lamis DA, Carolis A, Erbuto D, Girardi P, Pompili M. Long-acting injectable second-generation antipsychotics improve negative symptoms and suicidal ideation in recent diagnosed schizophrenia patients: a 1-year follow-up pilot study. Schizophr Res Treat. 2018. https://doi.org/10.1155/2018/4834135.
21. Carr CN, Hall CP, Roche-Desilets JE, Burant CJ, Fuller MA. Evaluation of adherence in patients prescribed long-acting injectable antipsychotics: a comparison of biweekly versus monthly administered neuroleptics. Ment Health Clin. 2016;6(5):248–53. https://doi.org/10.9740/mhc.2016.09.248.
22. Guillon P, Harmand S, Ansolabehere X. Real-life persistence of long-acting injectable antipsychotics in schizophrenic patients: a retrospective observational study in France. Int J Clin Pharmacol Ther. 2019;57(9):437–44. https://doi.org/10.5414/CP203427.
23. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational

Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. J Clin Epidemiol. 2008;61:344–9. https://doi.org/10.1016/j.jclinepi.2007.11.008.
24. Martínez-Andrés JA, García-Carmona JA. Clozapine, a controversial gold standard antipsychotic for the 21st century: switching to paliperidone palmitate 3-monthly improves the metabolic profile and lowers antipsychotic dose equivalents in a treatment-resistant schizophrenia cohort. Schizophr Res. 2019;212:234–6.
25. Leucht S, Samara M, Heres S, et al. Dose equivalents for second-generation antipsychotic drugs: the classical mean dose method. Schizophr Bull. 2015;41:1397–402.
26. Ashton CH. Benzodiazepines: how they work and how to withdrawn. Paperback, 2006.
27. Villa LF. Medimecum guía de terapia farmacológica. Ed Medilogic 2016.
28. Saavedra J, López M, González S, Arias S, Crawford P. Cognitive and social functioning correlates of employment among people with severe mental illness. Community Ment Health J. 2016;52(7):851–8. https://doi.org/10.1007/s10597-015-9874-4.
29. Instituto Nacional Estadística. Encuesta Nacional de Salud 2017. MSCBS-INE.
30. Mallet J, Le Strat Y, Schürhoff F, Mazer N, Portalier C, Andrianarisoa M, Aouizerate B, Berna F, Brunel L, Capdevielle D, Chereau I, D'Amato T, Denizot H, Dubreucq J, Faget C, Gabayet F, Lançon C, Llorca PM, Misdrahi D, Rey R, Roux P, Schandrin A, Urbach M, Vidailhet P, Fond G, Dubertret C. Cigarette smoking and schizophrenia: a specific clinical and therapeutic profile? Results from the FACE-Schizophrenia cohort. Prog Neuropsychopharmacol Biol Psychiatry. 2017;79:332–9. https://doi.org/10.1016/j.pnpbp.2017.06.026.
31. Hunt GE, Large MM, Cleary M, Lai HMX, Saunders JB. Prevalence of comorbid substance use in schizophrenia spectrum disorders in community and clinical settings, 1990–2017: systematic review and meta-analysis. Drug Alcohol Depend. 2018;191:234–58.
32. Victoroff J, Coburn K, Reeve A, Sampson S, Shillcutt S. Pharmacological management of persistent hostility and aggression in persons with schizophrenia spectrum disorders: a systematic review. J Neuropsychiatry Clin Neurosci. 2014;26(4):283–312. https://doi.org/10.1176/appi.neuropsych.13110335.
33. Buoli M, Rovera C, Esposito CM, Grassi S, Cahn W, Altamura AC. The use of long-acting antipsychotics for the management of aggressiveness in schizophrenia: a clinical overview. Clin Schizophr Relat Psychoses. 2018. https://doi.org/10.3371/csrp.buro.061518.
34. Musil R, Obermeier M, Russ P, Hamerle M. Weight gain and antipsychotics: a drug safety review. Expert Opin Drug Saf. 2015;14(1):73–96. https://doi.org/10.1517/14740338.2015.974549.
35. Huhn M, Nikolakopoulou A, Schneider-Thoma J, Krause M, Samara M, Peter N, Arndt T, Bäckers L, Rothe P, Cipriani A, Davis J, Salanti G, Leucht S. Comparative efficacy and tolerability of 32 oral antipsychotics for the acute treatment of adults with multi-episode schizophrenia: a systematic review and network meta-analysis. Lancet. 2019;394:939–51. https://doi.org/10.1016/S0140-6736(19)31135-3.
36. Ribeiro ELA, de Lima Mendonça T, Vieira MEB, Storpirtis S, Aguiar PM. Efficacy and safety of aripiprazole for the treatment of schizophrenia: an overview of systematic reviews. Eur J Clin Pharmacol. 2018;74(10):1215–33. https://doi.org/10.1007/s00228-018-2498-1.
37. Lähteenvuo M, Tanskanen A, Taipale H, Hoti F, Vattulainen P, Vieta E, Tiihonen J. Real-world effectiveness of pharmacologic treatments for the prevention of rehospitalization in a finnish nationwide cohort of patients with bipolar disorder. JAMA Psychiatry. 2018;75(4):347–55. https://doi.org/10.1001/jamapsychiatry.2017.4711.
38. Stone JM, Roux S, Taylor D, Morrison PD. First-generation *versus* second-generation long-acting injectable antipsychotic drugs and time to relapse. Ther Adv Psychopharmacol. 2018;8(12):333–6. https://doi.org/10.1177/2045125318795130.
39. Patel R, Chesney E, Taylor M, Taylor D, McGuire P. Is paliperidone palmitate more effective than other long-acting injectable antipsychotics? Psychol Med. 2018;48(10):1616–23. https://doi.org/10.1017/S0033291717003051.
40. Fleischhacker WW, Kane JM, Geier J, et al. Completed and attempted suicides among 18,154 subjects with schizophrenia included in a large simple trial. J Clin Psychiatry. 2014;75(3):e184–90.
41. Windfuhr K, Kapur N. Suicide and mental illness: a clinical review of 15 years findings from the UK National Confidential Inquiry into Suicide. Br Med Bull. 2011;100:101–21. https://doi.org/10.1093/bmb/ldr042.
42. Suominen KH, Isometsä ET, Henriksson MM, Ostamo AI, Lönnqvist JK. Suicide attempts and personality disorder. Acta Psychiatr Scand. 2000;102(2):118–25.
43. Hunt I, Kapur N, Robinson J, et al. Suicide within 12 months of mental health service contact in different age and diagnostic groups. Br J Psychiatry. 2006;188:135–42.
44. Corigliano V, Comparelli A, Mancinelli I, Montalbani B, Lamis DA, Carolis A, Erbuto D, Girardi P, Pompili M. Long-acting injectable second-generation antipsychotics improve negative symptoms and suicidal ideation in recent diagnosed schizophrenia patients: a 1-year follow-up pilot study. Schizophr Res Treat. 2018. https://doi.org/10.1155/2018/4834135.
45. Pompili M, Orsolini L, Lamis DA, Goldsmith DR, Nardella A, Falcone G, Corigliano V, Luciano M, Fiorillo A. Suicide prevention in schizophrenia: do long-acting injectable antipsychotics (LAIs) have a role? CNS Neurol Disord Drug Targets. 2017;16(4):454–62.
46. Sim F, Sweetman I, Kapur S, Patel MX. Re-examining the role of benzodiazepines in the treatment of schizophrenia: a systematic review. J Psychopharmacol. 2015;29(2):212–23. https://doi.org/10.1177/0269881114541013.
47. Tiihonen J, Suokas JT, Suvisaari JM, Haukka J, Korhonen P. Polypharmacy with antipsychotics, antidepressants, or benzodiazepines and mortality in schizophrenia. Arch Gen Psychiatr. 2012;69:476–83.
48. Leucht S, Cipriani A, Spineli L, Mavridis D, Orey D, Richter F, Samara M, Barbui C, Engel RR, Geddes JR, Kissling W, Stapf MP, Lässig B, Salanti G, Davis JM. Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. Lancet. 2013;382(9896):951–62. https://doi.org/10.1016/S0140-6736(13)60733-3.
49. Jariyavilas A, Thavichachart N, Kongsakon R, Chantakarn S, Arunpongpaisal S, Chantarasak V, Jaroensook P, Kittiwattanagul K, Nerapusee O. Effects of paliperidone extended release on hostility among Thai patients with schizophrenia. Neuropsychiatr Dis Treat. 2017;13:141–6. https://doi.org/10.2147/NDT.S112063.
50. Thomas JE, Caballero J, Harrington CA. The incidence of akathisia in the treatment of schizophrenia with aripiprazole, asenapine and lurasidone: a meta-analysis. Curr Neuropharmacol. 2015;13(5):681–91.
51. Miller CH, Fleischhacker WW. Managing antipsychotic-induced acute and chronic akathisia. Drug Saf. 2000;22(1):73–81.
52. Dimitropoulos E, Drogemuller L, Wong K. Evaluation of concurrent oral and long-acting injectable antipsychotic prescribing at the Minneapolis veterans affairs health care system. J Clin Psychopharmacol. 2017;37:5. https://doi.org/10.1097/JCP.0000000000000755.

53. Doshi JA, Pettit AR, Stoddard JJ, Zummo J, Marcus SC. Concurrent oral antipsychotic drug use among schizophrenia patients initiated on long-acting injectable antipsychotics post-hospital discharge. J Clin Psychopharmacol. 2015;35(4):442–6. https://doi.org/10.1097/JCP.0000000000000353.
54. Aggarwal NK, Sernyak MJ, Rosenheck RA. Prevalence of concomitant oral antipsychotic drug use among patients treated with long-acting, intramuscular, antipsychotic medications. J Clin Psychopharmacol. 2012;32(3):323–8. https://doi.org/10.1097/JCP.0b013e31825244f6.
55. Chong SA, Mythily G, Remington G. Clinical characteristics and associated factors in antipsychotic-induced akathisia of Asian patients with schizophrenia. Schizophr Res. 2003;59:67–71.
56. Woods SW, Morgenstern H, Saksa JR, et al. Incidence of tardive dyskinesia with atypical versus conventional antipsychotic medications: a prospective cohort study. J Clin Psychiatry. 2010;71:463–74.
57. Young SL, Taylor M, Lawrie S. "First do no harm". A systematic review of the prevalence and management of antipsychotic adverse effects. J Psychopharmacol. 2014;1–10.

Evaluation of long-acting injectable antipsychotics with the corresponding oral formulation in a cohort of patients with schizophrenia: a real-world study in Spain

Juan Antonio García-Carmona[a,b]*, Jorge Simal-Aguado[c]*, María Pilar Campos-Navarro[d], Francisco Valdivia-Muñoz[e,f] and Alejandro Galindo-Tovar[c]

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To date, only a few studies compared some long-acting injectables (LAIs) antipsychotics showing similar symptom improvement, relapse rates and adherence to treatment. We evaluated the use of LAIs antipsychotics [aripiprazole-1-month (A1M); paliperidone-1-month and 3-month (PP1M and PP3M) and biweekly (2w)-LAIs] and their corresponding oral formulations through (1) the number of hospital re-admissions, (2) the number of documented suicidal behaviour/attempts and (3) the use of concomitant benzodiazepines, oral antipsychotics and biperiden. A total of 277 patients, ≥18 years old, were included if were treated with the corresponding oral or LAI antipsychotic during at least 12 months and were previously diagnosed with schizophrenia. Our results showed that LAIs associated significantly lower suicidal behaviour, reduced the number of hospital admissions, lower diazepam and haloperidol equivalents and mean daily dose of biperiden intake versus oral antipsychotics. Furthermore, significant differences were found between LAIs. Specifically, PP3M was associated to lower hospital admissions versus A1M; PP1M and PP3M lower doses of diazepam equivalents versus 2w-LAIs and finally, PP1M lower antipsychotic intake versus 2w-LAIs. In conclusion, LAIs improved clinical outcomes by reducing the need for concomitant treatments and hospital admissions over oral antipsychotics. PP1M and PP3M showed better outcomes versus A1M and biweekly LAIs. *Int Clin Psychopharmacol* 36: 18–24 Copyright © 2020 Wolters Kluwer Health, Inc. All rights reserved.

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Keywords: benzodiazepines, biperiden, hospital admission, long-acting injectable antipsychotics, oral antipsychotics, suicidal behaviour

[a]Department of Neurology, Santa Lucia University Hospital, Cartagena, [b]Unit of Acute Psychiatry, Reina Sofía University Hospital, [c]Department of Pharmacy, Health Sciences Faculty, San Antonio Catholic University of Murcia, UCAM, [d]Unit of Acute Psychiatry, Santa Lucia University Hospital, Cartagena, [e]Center of Mental Health Infante and [f]Center of Mental Health Cartagena, Cartagena, Murcia, Spain

Correspondence to Juan Antonio García-Carmona, MD, PhD, BPharm, Department of Neurology, Santa Lucía University Hospital, C/Mezquita s/n, 30202, Cartagena, Murcia, Spain
Tel/fax: +34 968 110 859; e-mail: dr.jagarcar@gmail.com

*Juan Antonio García-Carmona and Jorge Simal-Aguado contributed equally to the writing of this article.

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Introduction

Schizophrenia is a chronic-relapsing mental disorder with an estimated prevalence of 3–6/1000 inhabitants in Spain (Oliva-Moreno *et al.*, 2006; Moreno-Küstner *et al.*, 2016) and 1% worldwide (Andon *et al.*, 2008). Schizophrenia is characterized by acute or residual psychotic symptoms, social impairment and decreased quality of life (Harrison *et al.*, 2001; Marwaha *et al.*, 2009).

Antipsychotics are the main therapeutic treatment for psychotic symptoms which typically appear in patients suffering from schizophrenia. In addition, these patients often suffer anosognosia which gets them unaware of their disorder hindering the adherence to the treatment. In order to improve this adherence, antipsychotics were formulated, first as depot, and later as long-acting injectables (LAIs). First-generation LAIs include fluphenazine and zuclopenthixol which were developed in the 1960s and both available as 2-weekly formulations (Coutinho *et al.*, 2000; Maayan *et al.*, 2015). Second-generation LAI includes risperidone and olanzapine, available since 2003 and 2008, respectively, and are typically administered 2-weekly (Rainer, 2008; Heres *et al.*, 2014). In the last few years, aripiprazole (A1M) and paliperidone (PP1M) LAIs emerged as monthly formulations in 2013 and 2009, respectively (Raoufinia *et al.*, 2017; Morris and Tarpada, 2017). Paliperidone is also available as a 3-monthly (PP3M) formulation since 2015 (Savitz *et al.*, 2017).

There are no differences in terms of efficacy among antipsychotics, as recently published in a meta-analysis (Huhn *et al.*, 2019) comparing 32 oral antipsychotics. Nonetheless, another recent meta-analysis of 25 mirror-image studies found that LAIs were superior to oral antipsychotics for preventing psychiatric hospitalization (Kishimoto *et al.*, 2013). To date, only a few studies compared some LAIs showing similar symptom improvement and relapse rates (Pandina *et al.*, 2011; Li *et al.*, 2011; McEvoy *et al.*, 2014) and there are limited studies comparing monthly and biweekly

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LAIs showing similar adherence to treatment (Carr *et al.*, 2016; Guillon *et al.*, 2019).

Here, we present results from a cohort of patients from the Region of Murcia, Spain; aiming to evaluate the use of A1M, PP1M and PP3M, versus the 2-weekly LAIs and all of them compared with a cohort only treated by using oral antipsychotics, through the following clinical outcomes: (1) the number of hospital re-admissions, (2) the number of documented suicidal behaviour/attempts and (3) the use of concomitant treatments, including benzodiazepines, oral antipsychotics and biperiden; by using a retrospective observational study design with a protocol that matches the oral antipsychotic to the LAI group as previously described (Lafeuille *et al.*, 2013).

Methods

Study design

We designed a cross-sectional study, from 2015 to 2017, based on a representative sample of the adult and non-institutionalized patients diagnosed with schizophrenia in the Region of Murcia, Spain. Sampling details have been previously described elsewhere (García-Carmona *et al.*, 2020).

A total number of 277 patients, ≥18 years old, were included if were treated with the corresponding oral or LAI antipsychotic during at least 12 months, no other LAI were administered during this period, and were previously diagnosed with schizophrenia according to the Diagnostic and Statistical Manual of Mental Disorders-Fifth Edition guidelines. Exclusion criteria included institutionalized patients, use of two LAIs, intellectual disability or autistic spectrum disorders and patients with missing records or unable to confirm treatment continuation for 1 year. The present study was drawn up following the 'STrengthening the Reporting of OBservational studies in Epidemiology' Statement items (von Elm *et al.*, 2008).

Study measures

Data collected included demographical information such as age, sex, civil status, tobacco and other drugs use as well as clinical data such as the disorder, its evolution (years) and the LAI dosage (Table 1). Furthermore, we collected the number of hospital admissions, documented suicidal behaviour/attempts as well as the concomitant psychiatric medications, including the use of other antipsychotics, benzodiazepines and biperiden.

On one hand, the number of hospital admissions and the documented suicidal behaviour/attempts were collected under the treatment with the corresponding oral or LAI antipsychotic (1 year) and expressed as the corresponding percentage/year. On the other hand, the treatments were compared by using the mean daily dose of biperiden and calculating the daily dose equivalents of antipsychotics and benzodiazepines by using haloperidol or diazepam as standards to compare the corresponding doses as previously published by the authors (Martínez-Andrés and García-Carmona, 2019) using tables of equivalences (Ashton, 2006; Leucht *et al.*, 2015; Villa, 2016).

Statistical analysis and confounding factors

All values are expressed as the mean ± SEM. All statistical analyses were performed using SPSS statistics v. 20 (IBM, Armonk, New York, USA). We set the LAI or the oral treatment as independent variables and the number of hospital admissions (%), the documented suicidal behaviour/attempts (%), biperiden and diazepam or haloperidol equivalents as dependent variables. Chi-square and Fischer's tests were used to analyze qualitative variables. Student's *t*-test and Kruskal–Wallis test were used to contrast qualitative and quantitative variables. Multivariate and bivariate logistic regression models were used to examine the joint effect of factors (age, sex and disorder evolution) upon the main outcome. Model 1 examined the different LAIs by a multivariate logistic regression while Model 2 was used to compare oral antipsychotics versus LAIs treatments by a bivariate logistic regression. Differences with a P value <0.05 were considered significant.

Results

Sample basal characteristics are shown in Table 1. Patients in LAI group were significantly older (41.5 ± 0.7; $P = 0.035$)

Table 1 Patients' demographical data

	Global (n=277)	OAPs (n=65)	LAIs (n=212)	A1M (n=51)	PP1M (n=89)	PP3M (n=53)	2-w (n=20)	P value
Sex (%)								0.204/0.118
Women	102 (37)	26 (40)	76 (36)	20 (39)	30 (34)	18 (34)	8 (40)	
Men	175 (63)	39 (60)	136 (64)	31 (61)	59 (66)	41 (66)	12 (60)	
Age (years ± SEM)	40.7 ± 0.6	38.3 ± 1.2	41.5 ± 0.7	38.7 ± 1.4	42.8 ± 1.1	41.3 ± 1.5	43.3 ± 1.9	**0.035**/0.246
Disorder duration (years)	13.2 ± 0.7	7.7 ± 0.8	14.9 ± 0.7	12.4 ± 1.3	16.1 ± 1.2	15.1 ± 1.4	15.1 ± 1.7	**0.035**/0.160
Legal status (%)								0.919/0.994
Single	226 (82)	50 (77)	176 (83)	43 (84)	72 (81)	44 (83)	17 (85)	
Divorced/separated	27 (10)	8 (12)	19 (9)	4 (8)	8 (9)	5 (9)	2 (10)	
Coupled/married	24 (8)	7 (11)	17 (8)	4 (8)	9 (10)	4 (8)	1 (5)	
Tobacco and drugs (%)								0.166/0.621
Tobacco	153 (55)	35 (54)	118 (56)	27 (53)	50 (56)	30 (57)	11 (55)	
Other drugs	97 (35)	22 (34)	75 (35)	16 (32)	33 (37)	19 (36)	7 (35)	

Bold indicates significance of $P < 0.05$.

OAP, oral antipsychotics; LAIs, long-acting injectables; A1M, aripiprazole LAI; PP1M, paliperidone palmitate 1-month LAI; PP3M, paliperidone palmitate 3-month LAI; 2-w, biweekly LAIs (zuclopenthixol n=6; risperidone, n=10; olanzapine, n=2; fluphenazine: n=2). P=0.035 comparing LAIs versus oral groups.

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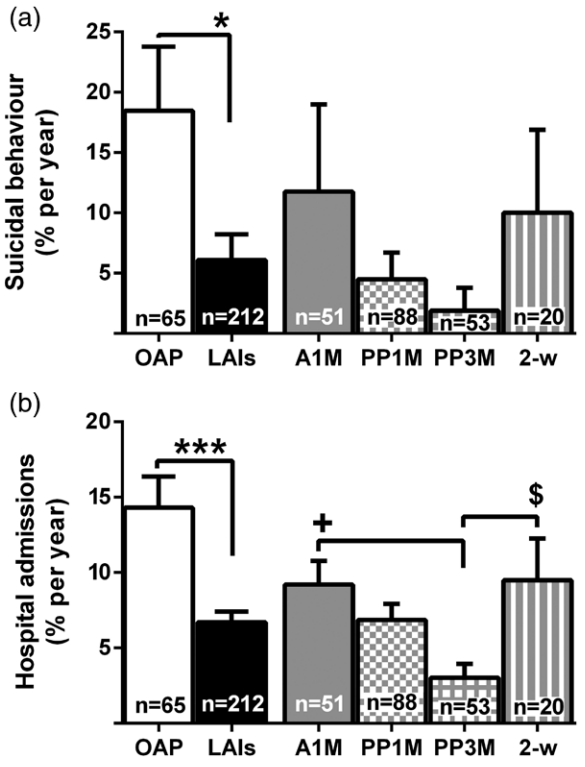
and with longest disease evolution (14.9 ± 0.7; $P = 0.035$) versus the patients treated with oral antipsychotics (38.3 ± 1.2; 7.7 ± 0.8). No other significant differences were found either between these groups or between LAIs. However, it is worth pointing out that 82% patients of the cohort were single and 10% divorced or separated. Moreover, 55% were smokers and 35% used illicit drugs.

Suicidal behaviour

The number of suicidal behaviour/attempts was expressed as the percentage/year for the period from 2015 to 2017 (Fig. 1a). Around 9% (9.3 ± 1.03) of the patients in this cohort showed suicidal behaviour. Bivariate analysis demonstrated (Table 2) that patients treated with LAIs (6.10 ± 2.11) associate a significantly (OR = 0.01, 95% CI, 0.01–0.02; $P = 0.043$) lower suicidal behaviour than patients treated with oral antipsychotics (18.46 ± 5.32). No significant differences were found between LAIs.

Hospital admissions

Fig. 1



Suicidal behaviour and hospital readmissions. (a) Suicidal behaviour (%), (b) hospital admissions (%) by oral and long-acting injectable (LAI) groups. Data are expressed as the mean ± SEM. Bivariate regression model: *$P<0.05$ and ***$P<0.001$ versus LAIs group. Multivariate regression model: +$P<0.05$ versus A1M; \$$P<0.05$ versus 2-w LAIs group. Abv: OAP, oral antipsychotics ($n=65$); LAIs, long-acting-injectables ($n=212$); A1M, aripiprazole-1-month ($n=51$); PP1M, paliperidone palmitate-1-month ($n=88$); PP3M, paliperidone palmitate-3-months ($n=53$), 2w-LAIs, biweekly-LAIs ($n=20$).

As shown in Fig. 1b and Table 2, the bivariate analysis revealed that LAIs (6.71 ± 0.78) significantly reduced (OR = 0.70; 95% CI, 0.34–1.05; $P = 0.001$) the number of hospital admissions over the oral-treated group (14.33 ± 2.1). Furthermore, significant differences were found between LAIs. Specifically, multivariate analysis demonstrated that patients treated with PP3M (3.02 ± 1.11) were significantly (OR=0.11, 95% CI, 0.04–0.26; $P = 0.041$), associated with lower hospital admissions versus A1M group (11.21 ± 0.92).

Psychiatric concomitant treatments

Concomitant treatments and LAI doses are summarized in Table 3. Statistical differences were found in the use of concomitant benzodiazepines. Specifically, the Chi-square test revealed a significantly higher number of benzodiazepines ($P = 0.001$; $\chi^2_{[df=1,276]} = 16.24$; relative risk = 3.30; 95% CI, 1.7–6.4) used by the oral-treated group in comparison with the LAI-treated group. Likewise, Fischer's test demonstrated a significantly ($P = 0.036$; $\chi^2_{[df=1,211]} = 8.54$) higher number of benzodiazepines used by the biweekly LAIs group when compared to the others LAIs. Despite being no statistical differences in the use of other concomitant treatments; there is a statistical trend in the use of the main antipsychotic as monotherapy ($P = 0.059$) treatment as well as in the number of concomitant antipsychotics ($P = 0.067$) between oral and LAIs groups.

In Fig. 2 is shown the data from the main concomitant oral medication in our cohort which mean daily dose was (mg/day): benzodiazepines (21.58 ± 1.99), antipsychotics (10.17 ± 0.79) and biperiden (1.09 ± 0.11). As shown in Table 2, bivariate analysis demonstrated that patients treated with LAIs associate a significantly lower diazepam (Fig. 2a; 18.11 ± 2.14; OR = 17.03; 95% CI, 7.29–26.76; $P = 0.001$) and haloperidol (Fig. 2b; 5.03 ± 0.58; OR = 21.77; 95% CI, 19.00–24.54; $P = 0.001$) equivalents and biperiden (Fig. 2c; 0.72 ± 0.11; OR = 1.45; 95% CI, 0.95–1.94; $P = 0.001$) intake versus patients receiving oral antipsychotics (32.94 ± 4.65; 27.02 ± 1.50; 2.28 ± 0.24; respectively). Moreover, significant differences were found between LAIs for diazepam (Fig. 2a) and haloperidol equivalents (Fig. 2b). Specifically, multivariate analysis (Table 2) showed significantly lower doses of diazepam equivalents with the use of PP1M (13.83 ± 2.48) and PP3M (10.70 ± 2.83) versus 2w-LAIs (43.00 ± 12.18; OR = 1.69, 95% CI, 0.99–6.38; $P = 0.048$). Furthermore, multivariate analysis revealed a significantly ($P = 0.015$) lower antipsychotic intake when comparing PP1M (3.69 ± 0.58) versus 2w-LAIs (11.10 ± 2.95; OR = 0.29; 95% CI, 0.06–0.53) group. Finally, no statistical differences were found when analyzing the concomitant intake of biperiden between LAIs groups (Fig. 2c).

Discussion

We found that patients in LAI group were older and with the longest disease duration. Both variables were included in further analysis to avoid biases.

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Table 2 Logistic regression analysis

	Model 1				Model 2		
	OR	95% CI	*P* value		OR	95% CI	*P* value
Diazepam equivalent							
Age	0.07	−0.71 to 0.57	0.826	Age	0.31	−0.30 to 0.92	0.322
Sex	7.53	−2.13 to 17.11	0.124	Sex	3.73	−4.92 to 12.37	0.397
Disease evolution	0.02	−0.66 to 0.63	0.953	Disease evolution	0.07	−0.72 to 0.59	0.836
LAIs	1.69	0.99 to 6.38	**0.048**	Oral versus LAIs	17.03	7.29 to 26.76	**0.001**
Haloperidol equivalent							
Age	−0.18	−0.35 to 0.01	0.059	Age	0.02	−0.34 to 0.02	0.058
Sex	−2.09	−4.66 to 0.47	0.109	Sex	2.80	−0.35 to 5.27	0.073
Disease evolution	0.22	−0.05 to 0.39	0.512	Disease evolution	0.17	−0.01 to 0.37	0.060
LAIs	0.29	0.06 to 0.53	**0.015**	Oral versus LAIs	21.77	19.00 to 24.54	**0.001**
Biperiden							
Age	−0.03	−0.06 to 0.03	0.075	Age	−0.04	−0.07 to 0.11	0.084
Sex	−0.20	−0.69 to 0.29	0.418	Sex	−0.15	−0.59 to 0.29	0.514
Disease evolution	0.02	−0.01 to 0.05	0.228	Disease evolution	0.02	−0.01 to 0.06	0.175
LAIs	0.96	−0.029 to 2.21	0.133	Oral versus LAIs	1,45	0.95 to 1.94	**0.001**
Suicide behaviour							
Age	−0.006	−0.01 to 0.00	0.056	Age	−0.01	−0.01 to 0.00	0.061
Sex	0.004	−0.09 to 0.1	0.932	Sex	0.02	−0.07 to 0.11	0.645
Disease evolution	0.003	−0.00 to 0.01	0.304	Disease evolution	0.003	−0.00 to 0.01	0.308
LAIs	−0.02	−0.06 to 0.03	0.498	Oral versus LAIs	0.099	0.01 to 0.02	**0.043**
Hospital admissions							
Age	0.001	−0.02 to 0.02	0.917	Age	−0.002	−0.03 to 0.02	0.839
Sex	0.01	−0.03 to 0.32	0.933	Sex	−0.06	−0.37 to 0.26	0.715
Disease evolution	−0.01	−0.03 to 0.01	0.267	Disease evolution	−0.01	−0.02 to 0.02	0.652
LAIs	0.11	0.04 to 0.26	**0.041**	Oral versus LAIs	0.70	0.34 to 1.05	**0.001**

Model 1: multivariate logistic regression comparing the different long-acting-injectable antipsychotics. Model 2: bivariate logistic regression comparing oral antipyschotic versus long-acting injectable antipsychotic treatments.
Bold indicates significance of $P < 0.05$.
CI, confidence interval; LAIs, long-acting injectable antipsychotics; OR, odds ratio.

Table 3 Use of concomitant oral psychodrugs

	Global (*n*=277)	OAPs (*n*=65)	LAIs (*n*=212)	A1M (*n*=51)	PP1M (*n*=88)	PP3M (*n*=53)	2-w (*n*=20)	*P* value
Dose mg/month±SEM				400±7	186±11	484±22 ψ	ψ	
Monotherapy (%)	45 (16)	6 (9)	39 (18)	5 (10)	18 (20)	14 (26)	2 (10)	0.059/0.113
N benzodiazepines (%)	181 (65)	56 (86)	125 (59)	29 (57)	55 (62)	23 (43)	18 (90)	**0.001/0.036**
1	126 (46)	40 (62)	86 (40)	16 (31)	40 (45)	18 (34)	12 (60)	
2	46 (17)	14 (22)	32 (15)	11 (22)	14 (16)	5 (9)	2 (10)	
3	9 (3)	2 (3)	7 (3)	2 (4)	1 (1)	–	4 (20)	
N antipsychotics (%)	232 (84)	59 (91)	173 (82)	46 (90)	70 (80)	39 (74)	18 (90)	0.067/0.113
1	181 (64)	36 (55)	145 (66)	36 (71)	62 (70)	36 (68)	11 (55)	
2	40 (16)	17 (26)	23 (14)	8 (15)	8 (9)	2 (4)	5 (25)	
3	11 (4)	6 (9)	5 (2)	2 (4)	–	1 (2)	2 (10)	
Biperiden (%)	67 (24)	16 (25)	41 (19)	7 (13.7)	20 (22.5)	7 (13.2)	7 (35.0)	0.338/0.107
Antidepressants (%)	64 (24)	14 (22)	50 (23)	8 (15.7)	25 (28.1)	12 (22.6)	5 (25.0)	0.884/0.399
1	53 (19)	12 (18)	41 (19)	8 (15.7)	18 (20.2)	11 (20.7)	4 (20.0)	
2	11 (5)	2 (4)	9 (4)	–	7 (7.9)	1 (1.9)	1 (5.0)	
Mood stabilizers (%)	39 (14)	9 (14)	30 (14)	4 (7.9)	17 (19.1)	4 (7.5)	5 (25.0)	0.965/0.162
1	37 (13)	8 (13)	29 (13)	3 (5.9)	17 (19.1)	4 (7.5)	5 (25.0)	
2	2 (1)	1 (1)	1 (1)	1 (2.0)	–	–	–	

A1M, aripiprazole LAI; OAP, oral antipsychotics; LAIs, long-acting injectable antipsychotics; PP1M, paliperidone palmitate 1-month LAI; PP3M, paliperidone palmitate 3-month LAI; 2-w, biweekly LAIs; Ψ, PP3M 3-month dose; 2-w LAIs doses: zuclopenthixol (192 mg, *n*=6; risperidone: 45 mg, *n*=10; olanzapine: 255 mg, *n*=2; fluphenazine: 25 mg, *n*=2).
Bold indicates significance of $P < 0.05$.

Nonetheless, it could indicate that patients would likely be treated first with oral antipsychotics but later, by non-compliance or other factors, with LAIs antipsychotics. In contrast, recent evidence suggests that treatment with LAIs can offer significant advantages over oral antipsychotics since the first episode of psychosis (Salgueiro and Segarra, 2019).

Moreover, schizophrenia is well known as a disorder causing severe social impairment (Nyer *et al.*, 2010; Szkultecka-Dębek *et al.*, 2016). In this line, our results indicate that more than 90% of patients are single or divorced. Tobacco use is particularly prevalent among individuals diagnosed with schizophrenia, with estimates ranging from 49 to 80% in the USA (Hughes, 1993; Lasser *et al.*, 2000; Poirier *et al.*,

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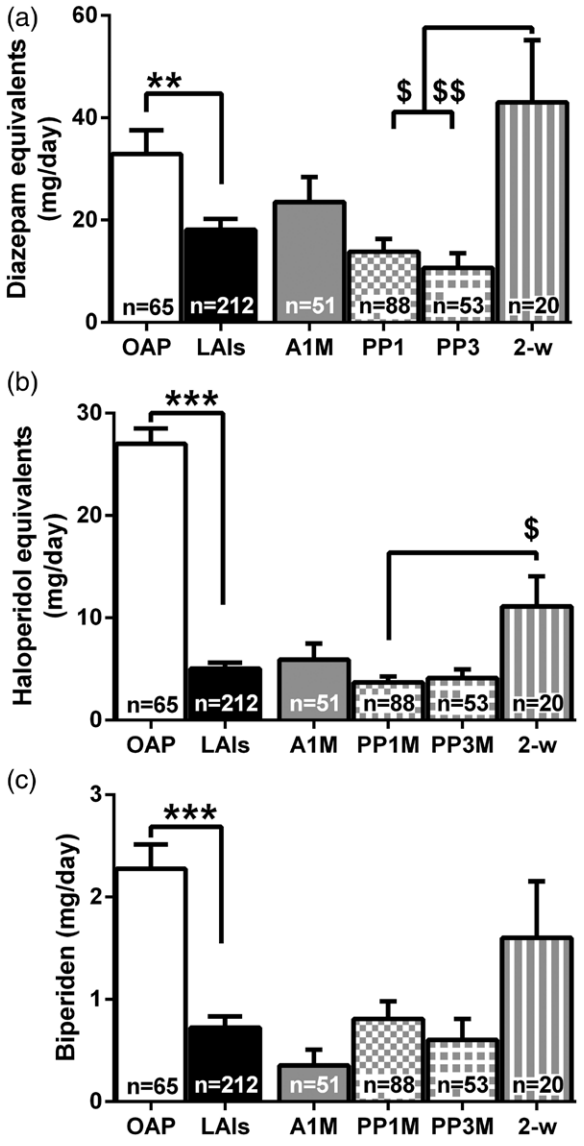
Fig. 2



Psychiatric concomitant treatments. Dose of psychiatric treatments (mg/day) of benzodiazepines and antipsychotics showed as diazepam (a) and haloperidol (b) equivalents; and biperiden (c) by oral and long-acting injectable (LAIs) groups. Data are expressed as the mean ± SEM. Bivariate regression model: $^{**}P<0.01$ and $^{***}P<0.001$ versus LAIs group. Multivariate regression model: $\$P<0.05$, $\$\$P<0.01$ versus 2-w LAIs. OAP, oral antipsychotics ($n=65$); LAIs, long-acting-injectables ($n=212$); A1M, aripiprazole-1-month ($n=51$); PP1M, paliperidone palmitate-1-month ($n=88$); PP3M, paliperidone palmitate-3-month ($n=53$); 2-w, biweekly-LAIs ($n=20$).

2002). According to these studies, we found a prevalence of 55% smokers but our data could be underestimated given tobacco and drug use are usually misreported in patients' clinical history. Furthermore, we found 30.6% of patients using illicit drugs like alcohol, cocaine, cannabis or amphetamines. This finding is consistent with a previous meta-analysis reporting 27.5% prevalence of illicit drug use in schizophrenia (Hunt *et al.*, 2018).

Suicidal behaviour

Half of the patients with schizophrenia show suicidal behaviour and 10% die by suicide during their lifetime. Our results showed that 9% of our patients showed suicidal behaviour per year and fortunately no one died. Similarly, Aydın *et al.* (2019) showed that 40.8% of schizophrenia patients attempted suicide at least once in 4 years in a cohort from Turkey. Furthermore, our results indicated that the use of LAIs reduced the risk of suicidal behaviour. Our results are in line with previous data showing that the use of LAIs reduces the risk of death by suicide when compared to the corresponding oral equivalent in an 8-year follow-up study (Tiihonen *et al.*, 2017). Antipsychotics, both oral and LAIs have been demonstrated useful for the management of aggression which could trigger suicidal behaviour (Mohr *et al.*, 2017; Bak *et al.*, 2019). Moreover, suicide risk has been associated with reduced adherence to the treatment and higher relapse rates (Pompili *et al.*, 2009) and it is probably the underlying mechanism by which LAIs show better outcomes than oral treatments in suicide prevention. Furthermore, LAIs are administered by a healthcare professional, which can strengthen the therapeutic relationship and therefore reduce the risk of suicide.

Hospital admissions

Our results demonstrated a lower risk of hospital readmissions in the LAI group compared to the oral antipsychotics group in a 1-year follow-up. Previous studies demonstrated a 20–30% reduced risk of hospital readmission during LAI treatment compared with the equivalent oral formulations (Tiihonen *et al.*, 2017) and a 5% lower risk of rehospitalisation at 60 days in the LAI group compared with oral antipsychotics (MacEwan *et al.*, 2016). Moreover, a recent meta-analysis of 42 studies (Kishimoto *et al.*, 2018) demonstrated that LAIs are associated with reduced rates of hospitalization compared to oral antipsychotics. Altogether, we suggest that LAIs reduce hospital admissions by improving compliance with the treatment and therefore, preventing relapses.

Concomitant treatments

Antipsychotic polypharmacy is defined as the simultaneous prescription of more than one antipsychotic medication (Shih-Ku, 2020). While polypharmacy is not actively recommended in clinical practice guidelines, it is remarkably common in clinical practice (Shih-Ku, 2020). In fact, only the 9 and 18% of the patients treated with the oral and LAI antipsychotics, respectively, were only treated with one drug. In this line, 84% of patients were treated with at least other antipsychotics different from the main one. Moreover, over 50% of patients were treated with benzodiazepines while 24% used antidepressants or biperiden. Our results showed higher rates regarding the use of antipsychotics respect previous large-scale studies showing 40–49% of patients treated with at least two antipsychotics (Wu *et al.*, 2011; Toto *et al.*, 2019).

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Nonetheless, our results are in line with previous studies showing 25–79% patients treated with benzodiazepines (Wu *et al.*, 2011; Chakos *et al.*, 2011; Toto *et al.*, 2019) 15–60% anticholinergics (Wu *et al.*, 2011; Chakos *et al.*, 2011; Toto *et al.*, 2019) 13–30% antidepressants (Wu *et al.*, 2011; Chakos *et al.*, 2011; Toto *et al.*, 2019) and 11–17% mood stabilizers (Wu *et al.*, 2011; Toto *et al.*, 2019; Dong *et al.*, 2019). Altogether, these results demonstrate that polypharmacy is more common than desirable in the treatment of schizophrenia, despite being no solid evidence supporting it (Correll *et al.*, 2017; Stroup *et al.*, 2019).

To the best of our knowledge, this is the first study comparing the prescription patterns and daily doses of concomitant benzodiazepines, antipsychotics and biperiden between oral and LAIs antipsychotics as well as between the LAIs. Our results demonstrated that the use of LAIs may reduce the use of concomitant benzodiazepines versus oral antipsychotic treatment. In this regard, antipsychotic treatment has been shown to significantly reduce anxiety when used as adjunctive therapy or monotherapy (Vulink *et al.*, 2011; Hershenberg *et al.*, 2014). As discussed below, we also suggest that clinicians would be more cautious when using LAIs and therefore wait more time until response and avoid adding more medication. Furthermore, our results showed a statistical trend to use lower number of concomitant antipsychotics as well as a significantly lower daily dose of antipsychotics when comparing the LAIs versus oral treatment groups. There is no evidence of a dose-response relationship with antipsychotics in the approved dose range. Nonetheless, we suggest clinicians tend to raise the dose until the response is observed when using oral antipsychotics whereas the use of LAIs requires more caution. We also hypothesize that LAIs may reduce the need for concomitant treatments due to its higher stable plasma levels and better adherence to the treatment.

Limits

Given our inclusion/exclusion criteria were not restrictive; our cohort could provide a high external validity to the western countries, in particular to Spain. Nonetheless, our study may have some less apparent biases. For example, some clinical data, such as tobacco and drugs, are often unrecorded. Sample size, specifically within LAIs comparison could be small to obtain conclusive results. Compliance with the LAIs was guaranteed given the treatment was administered by trained healthcare staff. However, adherence to the oral antipsychotics was assessed by prescriptions but plasma levels or pill counts were not available to check adherence. It is also possible that low-impact suicidal behaviour does not mean a visit to their psychiatrist or to the hospital. Furthermore, considering that the severity of each patient's condition was not available from hospital records, it is not possible to elucidate whether patients of LAI groups had a worse prognosis versus patients treated with oral antipsychotics. Several other reasons might be to follow an LAI instead of oral treatment. Furthermore, it is possible that patients treated with the newest LAIs had a better prognosis or required less frequent follow-up assessments compared with patients treated with 2-week LAIs. Finally, although hospital re-admissions is a useful marker of effectiveness, it is also more easily affected by other variables, such as the patient's social and family support, which are unrelated to the medication. Therefore, more studies including anxiety, anger, depression scales and prescriber habits are needed to truly establish the role of the newest LAIs versus biweekly and oral antipsychotics in schizophrenia.

Conclusion

In summary, this is the first study comparing the use of oral antipsychotics and their LAIs formulation regarding concomitant treatments. Despite the limitations of our study, we demonstrated that LAIs reduced the need for concomitant benzodiazepines and the daily dose of concomitant benzodiazepines and antipsychotics, as well as, the visits to the emergency department and hospital admissions over oral antipsychotics. Further research is needed to clarify the effects and interactions of LAIs; however, our findings could be useful for clinicians and their practice.

Acknowledgements

Ethics and methodology issues approval for the study was granted by both the research ethics committee of the Murcia Health Service and by the ethics committee of the San Antonio Catholic University of Murcia (UCAM) (CE031914). No identifiable information was retained or is presented in this manuscript. Informed consent was obtained from each patient prior to off-label treatment.

Conflicts of interest

There are no conflicts of interest.

References

Andon R, Keshavan MS, Nasrallah HA (2008). Schizophrenia, "just the facts": what we know in 2008 part 1: overview. *Schizophr Res* **100**:4–19.

Ashton CH (2006). *Benzodiazepines: how they work and how to withdrawn*. Paperback.

Aydın M, Ilhan BC, Tekdemir R, Çokünlü Y, Erbasan V, Altınbaş K (2019). Suicide attempts and related factors in schizophrenia patients. *Saudi Med J* **40**:475–482.

Bak M, Weltens I, Bervoets C, De Fruyt J, Samochowiec J, Fiorillo A, *et al.* (2019). The pharmacological management of agitated and aggressive behaviour: a systematic review and meta-analysis. *Eur Psychiatry* **57**:78–100.

Carr CN, Hall CP, Roche-Desilets JE, Burant CJ, Fuller MA (2016). Evaluation of adherence in patients prescribed long-acting injectable antipsychotics: a comparison of biweekly versus monthly administered neuroleptics. *Ment Health Clin* **6**:248–253.

Chakos M, Patel JK, Rosenheck R, Glick ID, Hammer MB, Tapp A, *et al.* (2011). Concomitant psychotropic medication use during treatment of schizophrenia patients: longitudinal results from the CATIE study. *Clin Schizophr Relat Psychoses* **5**:124–134.

Correll CU, Rubio JM, Inczedy-Farkas G, Birnbaum ML, Kane JM, Leucht S (2017). Efficacy of 42 pharmacologic cotreatment strategies added to antipsychotic monotherapy in schizophrenia: systematic overview and quality appraisal of the meta-analytic evidence. *JAMA Psychiatry* **74**:675–684.

Coutinho E, Fenton M, Quraishi S (2000). Zuclopenthixol decanoate for schizophrenia and other serious mental illnesses. *Cochrane Database Syst Rev* **1999**:CD001164.

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Dong M, Zeng LN, Zhang Q, Yang S-Y, Chen L-Y, Najoan E, *et al*. (2019). Prescription of antipsychotic and concomitant medications for adult Asian schizophrenia patients: findings of the 2016 Research on Asian Psychotropic Prescription Patterns (REAP) survey. *Asian J Psychiatr* **45**:74–80.

García-Carmona JA, Simal-Aguado J, Campos-Navarro MP, Valdivia-Muñoz F, Galindo-Tovar A (2020). Long acting-injectables antipsychotics: analysis of prescription patterns and patient's characteristics in mental health from a Spanish real-world study. *Clin Drug Invest* **40**:459–468.

Guillon P, Harmand S, Ansolabehere X (2019). Real-life persistence of long-acting injectable antipsychotics in schizophrenic patients: A retrospective observational study in France. *Int J Clin Pharmacol Ther* **57**:437–444.

Harrison G, Hopper K, Craig T, Laska E, Siegel C, Wanderling J, *et al*. (2001). Recovery from psychotic illness: a 15- and 25-year international follow-up study. *Br J Psychiatry* **178**:506–517.

Heres S, Kraemer S, Bergstrom RF, Detke HC (2014). Pharmacokinetics of olanzapine long-acting injection: the clinical perspective. *Int Clin Psychopharmacol* **29**:299–312.

Hershenberg R, Gros DF, Brawman-Mintzer O (2014). Role of atypical antipsychotics in the treatment of generalized anxiety disorder. *CNS Drugs* **28**:519–533.

Hughes JR (1993). Possible effects of smoke-free inpatient units on psychiatric diagnosis and treatment. *J Clin Psychiatry* **54**:109–114.

Huhn M, Nikolakopoulou A, Schneider-Thoma J, Krause M, Samara M, Peter N, *et al*. (2019). Comparative efficacy and tolerability of 32 oral antipsychotics for the acute treatment of adults with multi-episode schizophrenia: a systematic review and network meta-analysis. *Lancet* **394**:939–951.

Hunt GE, Large MM, Cleary M, Lai HMX, Saunders JB (2018). Prevalence of comorbid substance use in schizophrenia spectrum disorders in community and clinical settings, 1990-2017: systematic review and meta-analysis. *Drug Alcohol Depend* **191**:234–258.

Kishimoto T, Hagi K, Nitta M, Leucht S, Olfson M, Kane JM, Correll CU (2018). Effectiveness of long-acting injectable vs oral antipsychotics in patients with schizophrenia: a meta-analysis of prospective and retrospective cohort studies. *Schizophr Bull* **44**:603–619.

Kishimoto T, Nitta M, Borenstein M, Kane JM, Correll CU (2013). Long-acting injectable versus oral antipsychotics in schizophrenia: a systematic review and meta-analysis of mirror-image studies. *J Clin Psychiatry* **74**:957–965.

Lafeuille MH, Laliberté-Auger F, Lefebvre P, Frois C, Fastenau J, Duh MS (2013). Impact of atypical long-acting injectable versus oral antipsychotics on rehospitalization rates and emergency room visits among relapsed schizophrenia patients: a retrospective database analysis. *BMC Psychiatry* **13**:221.

Lasser K, Boyd JW, Woolhandler S, Himmelstein DU, McCormick D, Bor DH (2000). Smoking and mental illness: a population-based prevalence study. *JAMA* **284**:2606–2610.

Leucht S, Samara M, Heres S, Patel MX, Furukawa T, Cipriani A, *et al*. (2015). Dose equivalents for second-generation antipsychotic drugs: the classical mean dose method. *Schizophr Bull* **41**:1397–1402.

Li H, Rui Q, Ning X, Xu H, Gu N (2011). A comparative study of paliperidone palmitate and risperidone long-acting injectable therapy in schizophrenia. *Prog Neuropsychopharmacol Biol Psychiatry* **35**:1002–1008.

Maayan N, Quraishi SN, David A, Jayaswal A, Eisenbruch M, Rathbone J, *et al*. (2015). Fluphenazine decanoate (depot) and enanthate for schizophrenia. *Cochrane Database Syst Rev* **2**:CD000307.

MacEwan JP, Kamat SA, Duffy RA, Seabury S, Chou JW, Legacy SN, *et al*. (2016). Hospital readmission rates among patients with schizophrenia treated with long-acting injectables or oral antipsychotics. *Psychiatr Serv* **67**:1183–1188.

Martínez-Andrés JA, García-Carmona JA (2019). Clozapine, a controversial gold standard antipsychotic for the 21st century: switching to paliperidone palmitate 3-monthly improves the metabolic profile and lowers antipsychotic dose equivalents in a treatment-resistant schizophrenia cohort. *Schizophr Res* **212**:234–236.

Marwaha S, Johnson S, Bebbington PE, Angermeyer MC, Brugha TS, Azorin JM, *et al*. (2009). Predictors of employment status change over 2 years in people with schizophrenia living in Europe. *Epidemiol Psichiatr Soc* **18**:344–351.

McEvoy JP, Byerly M, Hamer RM, Dominik R, Swartz MS, Rosenheck RA, *et al*. (2014). Effectiveness of paliperidone palmitate vs haloperidol decanoate for maintenance treatment of schizophrenia: a randomized clinical trial. *JAMA* **311**:1978–1987.

Mohr P, Knytl P, Voráčková V, Bravermanová A, Melicher T (2017). Long-acting injectable antipsychotics for prevention and management of violent behaviour in psychotic patients. *Int J Clin Pract* **71**:e12997.

Moreno-Küstner B, Mayoral F, Navas-Campaña D, García-Herrera JM, Angona P, Martín C, Rivas F (2016). Prevalence of schizophrenia and related disorders in Malaga (Spain): results using multiple clinical databases. *Epidemiol Psychiatr Sci* **25**:38–48.

Morris MT, Tarpada SP (2017). Long-acting injectable paliperidone palmitate: a review of efficacy and safety. *Psychopharmacol Bull* **47**:42–52.

Nyer M, Kasckow J, Fellows I, Lawrence EC, Golshan S, Solorzano E, Zisook S (2010). The relationship of marital status and clinical characteristics in middle-aged and older patients with schizophrenia and depressive symptoms. *Ann Clin Psychiatry* **22**:172–179.

Oliva-Moreno J, López-Bastida J, Osuna-Guerrero R, Montejo-González AL, Duque-González B (2006). The costs of schizophrenia in Spain. *Eur J Health Econ* **7**:182–188.

Pandina G, Lane R, Gopal S, Gassmann-Mayer C, Hough D, Remmerie B, Simpson G (2011). A double-blind study of paliperidone palmitate and risperidone long-acting injectable in adults with schizophrenia. *Prog Neuropsychopharmacol Biol Psychiatry* **35**:218–226.

Poirier MF, Canceil O, Baylé F, Millet B, Bourdel MC, Moatti C, *et al*. (2002). Prevalence of smoking in psychiatric patients. *Prog Neuropsychopharmacol Biol Psychiatry* **26**:529–537.

Pompili M, Serafini G, Del Casale A, Rigucci S, Innamorati M, Girardi P, *et al*. (2009). Improving adherence in mood disorders: the struggle against relapse, recurrence and suicide risk. *Expert Rev Neurother* **9**:985–1004.

Rainer MK (2008). Risperidone long-acting injection: a review of its long term safety and efficacy. *Neuropsychiatr Dis Treat* **4**:919–927.

Raoufinia A, Peters-Strickland T, Nylander AG, Baker R, Eramo A, Jin N, *et al*. (2017). Aripiprazole once-monthly 400 mg: comparison of pharmacokinetics, tolerability, and safety of deltoid versus gluteal administration. *Int J Neuropsychopharmacol* **20**:295–304.

Salgueiro M, Segarra R (2019). Long-acting injectable second-generation antipsychotics in first-episode psychosis: a narrative review. *Int Clin Psychopharmacol* **34**:51–56.

Savitz A, Xu H, Gopal S, Nuamah I, Ravenstijn P, Janik A, *et al*. (2017). Efficacy and safety of paliperidone palmitate 3-month formulation for patients with schizophrenia: a randomized, multicenter, double-blind, noninferiority study. *Int J Neuropsychopharmacol* **19**:pyw018.

Shih-Ku L (2020). Antipsychotic polypharmacy: a dirty little secret or a fashion? *Int J Neuropsychopharmacol* **23**:125–131.

Stroup TS, Gerhard T, Crystal S, Huang C, Tan Z, Wall MM, *et al*. (2019). Comparative effectiveness of adjunctive psychotropic medications in patients with schizophrenia. *JAMA Psychiatry* **76**:508–515.

Szkultecka-Dębek M, Miernik K, Stelmachowski J, Jakovljević M, Jukić V, Aadamsoo K, *et al*. (2016). Schizophrenia causes significant burden to patients' and caregivers' lives. *Psychiatr Danub* **28**:104–110.

Tiihonen J, Mittendorfer-Rutz E, Majak M, Mehtälä J, Hoti F, Jedenius E, *et al*. (2017). Real-world effectiveness of antipsychotic treatments in a nationwide cohort of 29 823 patients with schizophrenia. *JAMA Psychiatry* **74**:686–693.

Toto S, Grohmann R, Bleich S, Frieling H, Maier HB, Greil W, *et al*. (2019). Psychopharmacological treatment of schizophrenia over time in 30 908 inpatients: data from the AMSP study. *Int J Neuropsychopharmacol* **22**:560–573.

Villa LF (2016). *Medimecum guía de terapia farmacológica*. Barcelona, Spain: Ed Medilogic.

von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP (2008). The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. *J Clin Epidemiol* **61**:344–349.

Vulink NC, Figee M, Denys D (2011). Review of atypical antipsychotics in anxiety. *Eur Neuropsychopharmacol* **21**:429–449.

Wu CS, Lin YJ, Liu SK (2011). Benzodiazepine use among patients with schizophrenia in Taiwan: a nationwide population-based survey. *Psychiatr Serv* **62**:908–914.

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Off-label use of second-generation antipsychotics in borderline personality disorder: a comparative real-world study among oral and long-acting injectables in Spain

Juan Antonio García-Carmona[a,b,*], Jorge Simal-Aguado[c,*], María Pilar Campos-Navarro[d], Francisco Valdivia-Muñoz[e,f] and Alejandro Galindo-Tovar[c]

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The aim of the present study was to evaluate the use of oral vs. long-acting injectables (LAIs) antipsychotics, as well as, to compare the effectiveness of different LAI antipsychotics [aripiprazole-1-month, paliperidone-1-month (PP1M), paliperidone-3-month (PP3M) and risperidone long-acting injectable (RLAI)] in patients diagnosed with borderline personality disorder (BPD), by evaluating the following clinical outcomes: (1) the number of hospital admissions; (2) the number of documented suicidal behaviour/attempts; and (3) the use of concomitant treatments, including benzodiazepines, oral antipsychotics and biperiden. We included a total of 116 patients diagnosed with BPD and treated with antipsychotic medication: 50 using a LAI antipsychotic formulation and 66 using the equivalent main oral antipsychotic. Patients treated with LAIs showed a decreased ratio of visits to emergency compared with the oral treatment group, and between LAIs, PP3M vs. aripiprazole-1-month group. Furthermore, patients treated with LAIs used lower number and dose of concomitant antipsychotics compared with patients treated with oral antipsychotics. Moreover, PP1M and PP3M used lower daily dose of diazepam equivalents compared with the aripiprazole-1-month and RLAI treatment groups. In conclusion, the use of LAIs may play a role in the management of BPD. *Int Clin Psychopharmacol* **36: 201–207** **Copyright © 2021 Wolters Kluwer Health, Inc. All rights reserved.**

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[a]Department of Neurology, Santa Lucia University Hospital, Cartagena, [b]Unit of Acute Psychiatry, Reina Sofía University Hospital, [c]Department of Pharmacy, Health Sciences Faculty, San Antonio Catholic University of Murcia, UCAM, [d]Unit of Acute Psychiatry, Santa Lucia University Hospital, Cartagena, [e]Centre of Mental Health Infante and [f]Centre of Mental Health Cartagena, Cartagena, Murcia, Spain

Correspondence to Juan Antonio García-Carmona, Department of Neurology, Santa Lucía University Hospital, C/Mezquita s/n, 30202, Cartagena, Murcia, Spain
Tel/fax: +34 968 110 859; e-mail: dr.jagarcar@gmail.com

*Juan Antonio García-Carmona and Jorge Simal-Aguado contributed equally to the writing of this article.

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Introduction

Borderline personality disorder (BPD) is a common, but not well understood, mental disorder characterized by disturbances in self-image, emotional dysregulation, impulsivity and impaired interpersonal relationships (Leichsenring *et al.*, 2011; APA, 2013). Furthermore, BPD patients show high rates of self-injury, suicidal ideation, severe functional impairment and other comorbid mental disorders (Huang *et al.*, 2009). BPD prevalence is 1–10% in the USA and Western countries (Torgersen *et al.*, 2001; Samuels *et al.*, 2002), more common in young adults (20–44 years), with no reported sex differences (Grant *et al.*, 2008; Stepp *et al.*, 2016).

Pharmacotherapy is often administered as an adjunctive treatment for BPD patients especially during periods of acute decompensation characterized by enhanced anxiety, aggressive/impulsive behaviour and psychotic-like symptoms (APA, 2001). Psychotic-like symptoms occur in 60% of BPD patients and include hallucinations, body-image distortions and ideas of reference or hypnagogic phenomena (Slotema *et al.*, 2018, D'Agostino *et al.*, 2019).

Only few studies have evaluated the role of antipsychotics in the treatment of BPD. Haloperidol was shown to be more effective than amitripityline for hostility (Soloff et al., 1986, 1989), while phenelzine was reported to be more effective than haloperidol for the treatment of depression and anxiety symptoms in BPD patients (Soloff *et al.*, 1993). Regarding atypical antipsychotics, clinical trials showed that olanzapine is effective in the management of anger and anxiety (Zanarini and Frankenburg, 2001; Bogenschutz and Nurnberg, 2004) and more effective compared with fluoxetine for relieving symptoms of depression and impulsive aggression (Zanarini *et al.*, 2004a). Nonetheless, no differences were shown neither between ziprasidone vs. placebo (Pascual *et al.*, 2008)

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Table 1 **Patient's sociodemographic data**

	No LAI, n = 66	LAIs, n = 50	*P*-value, χ^2, Student-*t*	AM, n = 17	PP1M, n = 16	PP3M, n = 12	Ris, n = 5	*P*-value, Fischer, Kruskal-W
Sex (%)			0.788					0.641
Women	30 (46)	23 (46)		10 (59)	7 (44)	4 (34)	2 (40)	
Men	36 (54)	27 (54)		7 (41)	9 (56)	8 (66)	3 (60)	
Age (y) ± SEM	42.4 ± 1.4	39.4 ± 1.7	0.179	39.4 ± 3.0	39.5 ± 2.9	38.8 ± 3.9	41.8 ± 8.1	0.977
Disorder evolution (y) ± SEM	9.9 ± 1.0	10.9 ± 1.3	0.563	8.9 ± 1.5	12.6 ± 2.7	8.8 ± 1.3	10.4 ± 2.9	0.525
Legal status (%)			0.500					0.684
Single/divorced	45 (69)	38 (76)		13 (76)	12 (75)	9 (75)	5 (100)	
Coupled/married	21 (31)	12 (24)		4 (24)	4 (25)	3 (25)	0 (0)	
Tobacco and drugs (%)								
Tobacco	29 (44)	24 (48)	0.521	9 (47)	7 (43)	5 (42)	3 (60)	0.870
Other drugs	22 (33)	15 (30)	0.706	5 (35)	5 (31)	3 (25)	2 (40)	0.946

In parenthesis (%) the corresponding percentage per group.
AM, aripiprazole-1-month; LAI, long-acting-injectable antipsychotic; PP1M, paliperidone palmitate-1-month; PP3M, paliperidone palmitate-3-month; Ris, risperidone-LAI; SEM, standard error media; y, years.

Table 2 **Concomitant treatments**

Dose (mg/monthly)	No LAI, n = 66 ND	LAIs, n = 50 ND	*P*-value, Chi^2	AM, n = 17 382.4	PP1M, n = 16 96.9	PP3M, n = 12 347.8[a]	Ris, n = 5 108.3[a]	*P*-value, Fischer
LAIs in monotherapy (%)	ND	5 (10)		1 (6)	2 (13)	2 (17)	ND	0.786
N benzodiazepines (%)	54 (82)	32 (64)	0.096	16 (94)	9 (56)	3 (25)	4 (80)	0.001
1	33 (50)	18 (36)		8 (47)	6 (38)	2 (17)	2 (40)	
2–3	21 (32)	14 (28)		8 (47)	3 (19)	1 (8)	2 (40)	
N antipsychotics (%)	49 (74)	27 (54)	0.008	12 (71)	8 (50)	5 (42)	3 (60)	0.533
1	28 (42)	19 (38)		8 (47)	7 (44)	2 (17)	2 (40)	
2–3	21 (32)	8 (16)		4 (24)	1 (6)	2 (16)	1 (20)	
Biperiden (%)	3 (5)	4 (8)	0.443	2 (12)	0 (0)	2 (17)	0 (0)	0.354
Antidepressants (%)	35 (53)	22 (44)	0.340	9 (53)	7 (44)	4 (34)	2 (40)	0.356
Mood stabilizer (%)	17 (26)	11 (22)	0.830	2 (12)	5 (32)	3 (25)	1 (20)	0.613

In parenthesis (%), the corresponding percentage per group.AM, aripiprazole-1-month; LAI, long-acting-injectable antipsychotic; ND, no data; PP1M, paliperidone palmitate-1-month; PP3M, paliperidone palmitate-3-month; Ris, risperidone-LAI.
[a]Three-month dose for PP3M and monthly dose for risperidone-LAI.

nor olanzapine compared with haloperidol (Shafti and Shahveisi, 2010) and asenapine (Bozzatello *et al.*, 2017) in emotional instability. A mirror-study showed that clozapine reduced psychiatric admissions and self-harm compared with previous antipsychotic treatments (Rohde *et al.*, 2018). Only one randomized controlled clinical trial was performed evaluating suicidal behaviour in BPD patients, showing a reduction of suicidal behaviour of flupenthixol depot compared with placebo (Montgomery and Montgomery, 1982).

Newest antipsychotics have scarcely been studied to date. In particular, aripiprazole has been shown to significantly reduce anger and anxiety in placebo-controlled trials (Nickel et al., 2006, 2007). Preliminary findings evaluating the effectiveness of long-acting injectable (LAI) antipsychotics such as risperidone long-acting injectable (RLAI) and paliperidone-1-month (PP1M) indicated that these drugs can effectively reduce aggression and anxiety in BPD patients (Bellino *et al.*, 2011; Carrasco *et al.*, 2012). Nonetheless, no studies have been reported comparing oral antipsychotics against the newest LAIs formulations or between them.

Therefore, the aim of the present study was to evaluate the use of oral vs. LAIs antipsychotics, as well as, to compare the effectiveness of different LAI antipsychotics [aripiprazole-1-month, PP1M, paliperidone-3-month (PP3M) and RLAI] in patients diagnosed with BPD, by evaluating the following clinical outcomes: (1) the number of hospital admissions; (2) the number of documented suicidal behaviour/attempts; and (3) the use of concomitant treatments, including benzodiazepines, oral antipsychotics and biperiden.

Methods

Study design

We designed a cross-sectional study, from 2015 to 2017, based on a representative sample of adult and non-institutionalized general population of the Murcia Region (Spain) as previously described by the authors (García-Carmona *et al.*, 2020). We included a total of 116 patients diagnosed with BPD and treated with antipsychotic medication: 50 using a LAI antipsychotic formulation and 66 using the equivalent main oral antipsychotic. Patients met the following inclusion criteria: ≥18-years-old, treated with the oral or LAI antipsychotic continuously for at least 12 months. In the study period, patients were not administered with other LAI than the first prescribed in this 1-year follow-up period, and were previously diagnosed with BPD according to the DSM-V guidelines. Exclusion criteria included (1) institutionalized patients and those who got institutionalized in a unit of chronic

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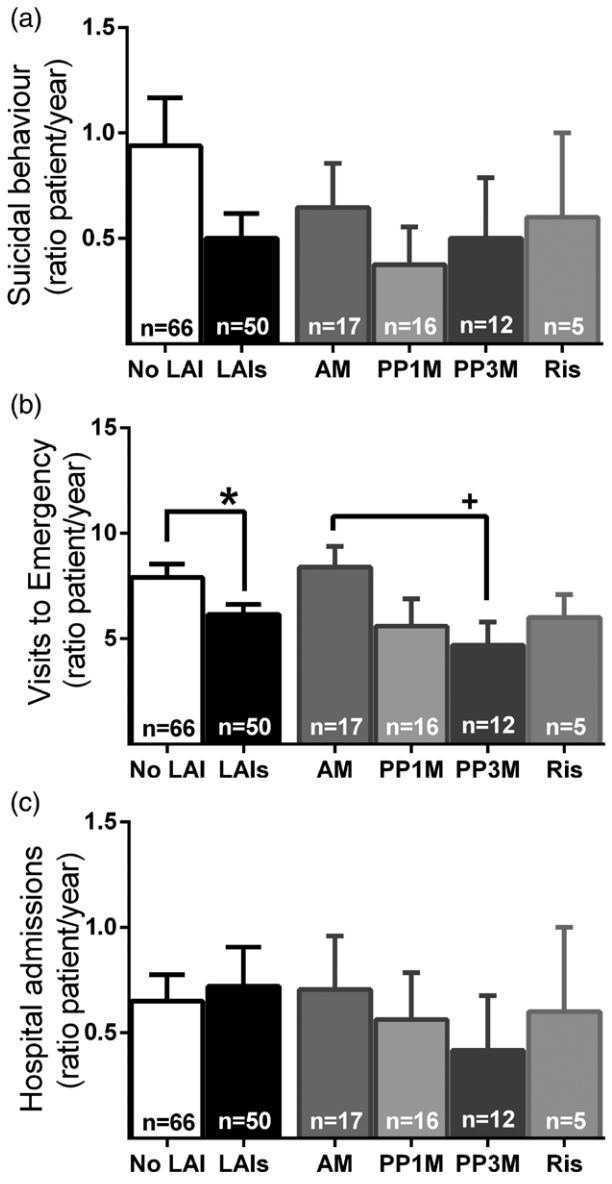
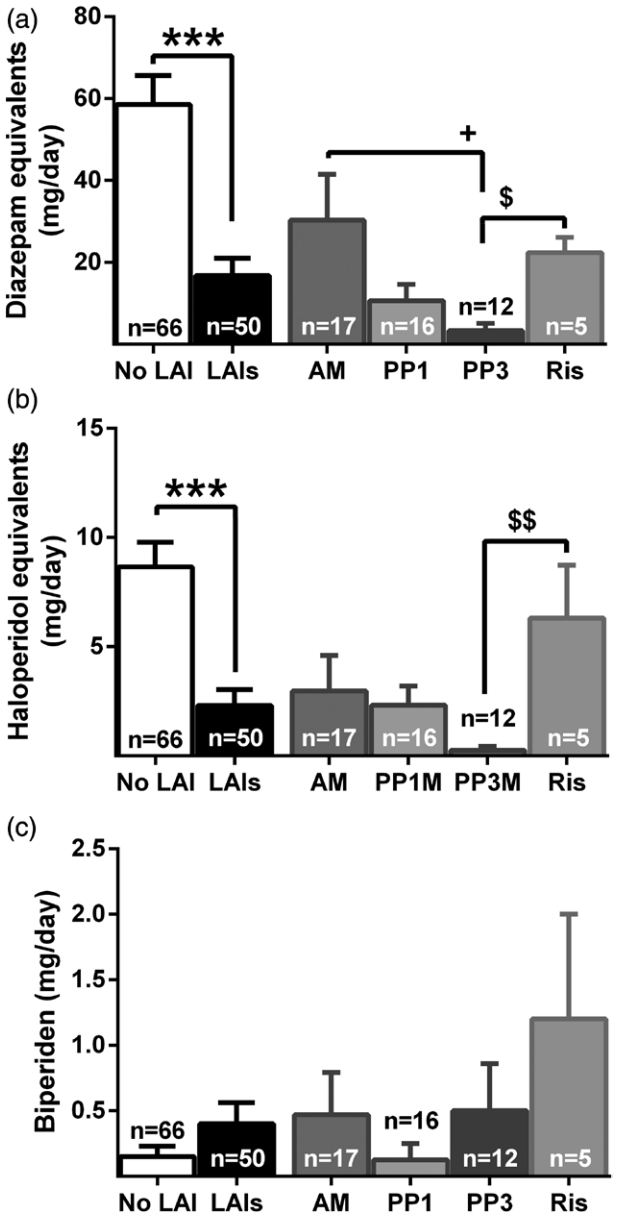
Fig. 1



Suicidal behaviour, visits to emergency and hospital readmissions. Mean of the ratio for patient and year about: (a) suicidal behaviour, (b) visits to emergency and (c) hospital admissions by oral and LAI groups. Data are expressed as the mean ± SEM. *$P < 0.05$ vs. LAIs group; +$P < 0.05$ vs. AM. AM, aripiprazole-1-month; LAI, long-acting-injectable antipsychotic; PP1M, paliperidone palmitate-1-month; PP3M, paliperidone palmitate-3-month, RLAI, risperidone-LAI.

Fig. 2



Psychiatric concomitant treatments. Dose of psychiatric treatments (mg/day) of benzodiazepines and antipsychotics showed as (a) diazepam and (b) haloperidol equivalents; and (c) biperiden by oral and LAIs groups. Data are expressed as the mean ± SEM. ***$P < 0.001$ vs. LAIs group; +$P < 0.05$ vs. AM, $$P < 0.05$, $$$P < 0.01$ vs. RLAI. AM, aripiprazole-1-month; LAI, long-acting-injectable antipsychotic; PP1M, paliperidone palmitate-1-month; PP3M, paliperidone palmitate-3-month, RLAI, risperidone-LAI.

psychiatry or other similar resources, (2) concomitant use of two LAIs, (3) intellectual disability, (4) concomitant psychiatric disorders and (5) patients with missing clinical records to confirm the use of a single treatment option and its follow-up during at least 1 year. The present study was designed following the 'strengthening the reporting of observational studies in epidemiology' (STROBE) statement items (Von Elm *et al.*, 2008).

Study measures

Data collected included demographical and clinical information such as age, sex, civil status, tobacco, drug use as well as the disorder duration (years) (Table 1). Concomitant treatments are summarized in Table 2, including the number of benzodiazepines, oral

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antipsychotics (excluding the main antipsychotic in both, oral/LAI groups), antidepressants, mood stabilizers or biperiden used. LAIs doses used are also reported in Table 2. Furthermore, we compared the rate of hospital admissions in the units of acute psychiatry and the visits to emergency department for psychiatric reasons (both variables showed as the ratio of the number of admissions or visits per patient/year). Moreover, we compared the suicidal behaviour (showed as ratio of the number of suicidal events/year for each patient). Suicidal behaviour was defined as a deliberate self-injury (including suicidal and nonsuicidal self-injury by any method: self-choking, poisoning, burning, cutting, etc.); suicidal ideation was not included in this parameter. To compare the use of concomitant treatments, we calculated the mean daily dose of biperiden and the daily dose equivalents of antipsychotics and benzodiazepines (mg/day) by using haloperidol or diazepam as standards to compare the corresponding doses as published elsewhere (Martínez-Andrés and García-Carmona, 2019).

Statistical analysis

Results are expressed as the mean ± SEM. All statistical analyses were performed using SPSS statistics v.20 (IBM, Armonk, NY, USA). Comparison of baseline characteristics between the oral and LAI groups was conducted using χ^2 or Student's *t*-tests while differences between LAIs were assessed by the Kruskal–Wallis or Fischer's (omnibus) tests followed by Bonferroni post-hoc test when appropriate. The effect of sex in suicidal behaviour, visits to emergency, hospital admissions and the concomitant treatment was assessed using Student's *t*-tests. All analyses were two-tailed and differences with a *P*-value <0.05 were considered significant. Full statistics are reported in Supplemental Table 3, Supplemental digital content 1, *http://links.lww.com/ICP/A83*.

Ethics approval

Ethics and methodology issues approval for the study were granted by both the Research Ethic Committee of the Murcia Health Service and by the Ethic Committee of the San Antonio Catholic University of Murcia (UCAM) (CE031914). No identifiable information was retained or is presented in this article. Informed consent was obtained from each patient prior off-label treatment.

Results

Baseline characteristics of the patients are reported in Table 1. No significant differences were found between groups based on the following parameters: sex, age, disease duration, civil status, tobacco and drug use. However, it is important to note that 69–76% of all patients were single or divorced, 44–48% reported to be smokers and more than 30% use illicit drugs. Concomitant treatments and LAIs dosage are summarized in Table 2. Only 10% of patients used LAIs as monotherapy with no differences between groups. Nonetheless, significant differences were found in the number of concomitant antipsychotics between our groups. Specifically, χ^2 test revealed a significantly higher number of concomitant antipsychotics ($P = 0.008$; $\chi^2_{[1,115]} = 7.268$) used in the oral-treatment group vs. the LAI-treatment group. Despite being no statistical differences in the number of concomitant benzodiazepines between oral and LAIs groups ($P = 0.096$, $\chi^2_{[1,115]} = 2.819$), Fischer's omnibus test demonstrated significant differences in the number of benzodiazepines between LAIs ($P = 0.001$; $F_{[df=1,49]} = 6.175$). In particular, Bonferroni post-hoc test revealed a significantly lower number of benzodiazepines used in both PP1M and PP3M groups compared with aripiprazole-1-month ($P = 0.045$, $P = 0.001$, respectively) and between the PP3M group compared to RLAI group ($P = 0.025$). Finally, no significant differences were found regarding the number of concomitant antidepressants, mood stabilizers and the use of biperiden between oral and LAIs groups ($P = 0.340$, $P = 0.830$, $P = 0.443$, respectively) nor between LAIs ($P = 0.356$, $P = 0.613$, $P = 0.354$, respectively).

Suicidal behaviour

The number of suicidal behaviour/attempts was expressed as the ratio of the number of patients showing this behaviour per year for the period from 2015 to 2017 (Fig. 1a). An average of 75.0% (±18.1) of the patients in this cohort showed suicidal behaviour. No statistical differences were found between women and men ($P = 0.112$). Moreover, no statistical differences were observed in the number of suicidal behaviours between patients using oral (9.39 ± 2.27) vs. LAIs antipsychotics (5.0 ± 1.19; $P = 0.1208$) and between the different LAIs ($P = 0.748$).

Visits to emergency and hospital admissions

No statistical differences were found between women and men in both the number of visits to emergency department ($P = 0.374$) or hospital admissions ($P = 0.191$). As shown in Fig. 1b, Student's *t*-test revealed that LAIs treatment (6.15 ± 0.48) significantly reduced ($t_{[1,115]} = 2.068$, $P = 0.0409$) the ratio of visits to emergency department compared with the oral antipsychotics treatment (7.90 ± 0.64). Furthermore, significant differences were found between the different LAIs antipsychotic treatments in respect to the number of visits to emergency departments. Specifically, Kruskal–Wallis followed by Bonferroni post-hoc test demonstrated that PP3M treatment was (4.70 ± 1.10) associated to lower ratio of patients visiting an emergency department vs. aripiprazole-1-month treatment (8.40 ± 0.98; $P = 0.0172$). Finally, no statistical differences between the different treatments groups were observed in the ratio of BPD patients admitted to a hospital (Fig. 1c).

Psychiatric concomitant treatments

In Fig. 2 shows the data from the main concomitant oral medication in our cohort, which means daily doses

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are diazepam equivalents (40.55 ± 5.87 mg/day), haloperidol equivalents (5.92 ± 0.95 mg/day) and biperiden (0.26 ± 0.11 mg/day). No sex differences were found in any of the concomitant treatments. Student's *t*-test revealed that patients treated with LAIs use significantly lower doses of diazepam equivalents compared with patients receiving oral antipsychotics (16.78 ± 4.27 vs. 58.55 ± 7.09, respectively; $t_{[1,115]} = 7.664$; $P = 0.0001$; Fig. 2a). Furthermore, Kruskal–Wallis test followed by Bonferroni post-hoc test showed significantly lower doses of diazepam equivalents concomitantly used with PP3M (3.33 ± 1.78 mg/day) compared with aripiprazole-1-month (30.294 ± 11.18; $P = 0.0379$) and RLAI (22.40 ± 3.709; $P = 0.0155$) treatment groups. In parallel, the LAIs treatment group used significantly ($P = 0.0001$) lower haloperidol equivalents doses (2.309 ± 0.7213 mg/day) vs. the oral treatment group (8.659 ± 1.122; $t_{[1,115]} = 4.339$); $P = 0.0001$; Fig. 2b). Moreover, Kruskal–Wallis test followed by Bonferroni post-hoc test revealed that PP3M significantly (0.751 ± 0.1794 mg/day) reduced antipsychotic intake compared with the RLAI (6.30 ± 2.427) group ($P = 0.0049$). No statistical differences were found between treatments in the biperiden intake (Fig. 2c).

Discussion

Recent studies have indicated that BPD patients show difficulties in social interaction and higher rates of drug use (Lis and Bohus, 2013; Shah and Zanarini, 2018). In agreement with previous reports (Torgersen *et al.*, 2001; Ullrich and Coid, 2009), our results show a rate of 69–76% single or divorced BPD patients. In addition, our results show that high rate of BPD patients were smoking tobacco products (44–48%) or using an illicit drug in their lives (30%). This finding is consistent with previous reports, which showed a range between 27% and 38% of BPD patients to also use illicit drugs (Crawford *et al.*, 2011; Martín-Blanco *et al.*, 2017).

Suicidal behaviour

In the present study, suicidal behaviour was prevalent in 75% of all patients during the during the study period. This finding is in line with previous data showing that approximately 80% of BPD patients show suicidal behaviour (Dubovsky and Kiefer, 2014). To the best of our knowledge, this is the first study assessing the role of different LAIs antipsychotics in suicidal behaviour of BPD. Although no statistical differences were observed between oral and LAIs groups, the rate of suicidal behaviour differs between these groups (0.94 ± 0.23 vs. 0.50 ± 0.12, respectively). To date, only few studies have been conducted to assess the role of some LAIs in BPD patients. Specifically, a study conducted by Palomares *et al.*, (2015) demonstrated that PP1M treatment reduces self-aggression behaviour when switching from oral paliperidone. Furthermore, two pilot studies have also reported that RLAI treatment was associated with significant clinical and functional improvement in symptoms associated with BPD, as compared with oral treatments; however, none of these studies have assessed RLAI in suicidal behaviours (Díaz-Marsá *et al.*, 2008; Carrasco *et al.*, 2012). Although antipsychotics may reduce, anxiety, anger and therefore can reduce suicidal behaviour, the use of LAIs formulations may further improve treatment adherence and exert superior effects in BPD patients to prevent suicide attempts. Nonetheless, additional larger and prospective studies are required to further confirm the effectiveness/efficacy of LAIs in suicide in this psychiatric population.

Visits to emergency department and hospital admissions

Our results demonstrated a decrease in the ratio of BPD patients visiting an emergency department (for psychiatric reasons) when treated with LAIs vs. oral antipsychotics; however, no differences were found between groups in hospital admissions (for psychiatric reasons). This difference between the visits to emergency department and hospital admission could be due to the speculation amongst clinicians that admission may be less effective and possibly harmful to patients diagnosed with personality disorders. Prior studies evaluated this issue in patients suffering from schizophrenia showing that LAIs reduced both the visits to emergency departments and hospital admissions (Fang *et al.*, 2020), whereas a more recent study showed that patients diagnosed with personality disorder were less likely to be admitted than other patients for suicidal behaviour (Van Veen *et al.*, 2019). Overall, we suggest that LAIs treatment may reduce potential visits to emergency rooms in BPD patients by reducing mood instability and aggressive behaviour. Moreover, LAIs can strengthen the therapeutic relationship between the patient and the clinician and therefore to reduce the visits to emergency department.

Concomitant treatments

The first main finding of the present study is that polypharmacy is a commonly used treatment strategy in BPD patients. Our results show that >50% of the patients were taking a combination of benzodiazepines, antipsychotics and antidepressants, while about 25% were taking mood stabilizers. These results are in line with previous reports, which showed that 40–50% of BPD patients were concomitantly using at least three medications (Zanarini *et al.*, 2004b; Crawford *et al.*, 2011; Paris, 2015).

A recent survey performed to Italian psychiatrists revealed that while oral antipsychotics are often prescribed off-label in ~50% of BPD patients, only 5–7% of the psychiatrists considered using a LAI formulation (Aguglia *et al.*, 2019). The scientific evidence for the use of antipsychotics in BPD is limited and provided by open-label, placebo-controlled or cross-sectional studies with small cohorts of patients. In fact, aripiprazole was found to significantly reduce anger, psychosis, impulsivity, as well

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as, depression and anxiety (Nickel *et al.*, 2006; Nickel *et al.*, 2007). Moreover, paliperidone improved impulsivity, anger, and dissociative symptoms (Bellino *et al.*, 2011). Similarly, risperidone was shown to improve hostility, suspicion, depression and anergia (Rocca *et al.*, 2002; Friedel *et al.*, 2008). Here, we directly compared, for the first time to our knowledge, the effects of different oral and LAIs antipsychotics in BPD patients. Our findings indicate that patients treated with LAIs use lower number and dose of concomitant antipsychotics compared with patients treated with oral antipsychotics. Moreover, PP1M and PP3M use lower daily dose of benzodiazepines compared with the aripiprazole-1-month and RLAI treatment groups, without any differences between groups in the number of antidepressants, mood stabilizers and biperiden used. Only a few studies compared LAIs and oral antipsychotics regarding their effects in the need of concomitant medications in BPD. In line with our findings, Palomares *et al.* (2015) showed reduced concomitant antipsychotics (from 56% to 25%) and benzodiazepines (from 81% to 56%) use when switching from oral paliperidone to PP1M treatment in BPD patients. Overall, our results suggest that the use of LAIs in BPD may reduce the need of concomitant oral antipsychotic treatments and the dose of concomitant of benzodiazepines.

LAIs are well known to improve treatment adherence but no prior studies have evaluated this issue in patients suffering from personality disorders. Given the long-lasting (weeks or even months) maladaptive symptoms occurring due to an extensive emotional instability in BPD patients, we speculate that LAIs will increase the adherence to the antipsychotic treatment regimes, which may improve emotional stability in these patients. Finally, it is worth mentioning that the BPD diagnosis is a challenge for clinicians and the widespread use of multiple treatments, specifically antipsychotics, may lead to misdiagnosis of comorbid neuropsychiatric diseases, such as bipolar disorder or psychotic spectrum disorders.

Limitations

The main limitations of the study include its nonrandomised open treatment design as well as the small simple size and its retrospective analysis. Given that our inclusion/exclusion criteria were not restrictive; our cohort could provide a high external validity to the western countries, including Spain. Nonetheless, our patients had no comorbid psychiatric diagnosis, which is common in BPD. Furthermore, our study may have some less apparent biases. First, we did not observe any sex differences in our outcomes. In this regard, it is possible that sex differences were not revealed due to the small size used in the present study. Second, some clinical data, such as tobacco and illicit drug use, are often unrecorded. Therefore, the prevalence of smoking, drug user and suicidal behaviour could be underestimated in our study. Third, it is also possible that low-impact suicidal behaviour does not mean a visit to their psychiatrist or to the emergency department. Furthermore, considering that the severity of each patient's condition was not available from hospital records, it is not possible to elucidate whether patients of LAI groups had a worse prognosis compared with patients treated with oral antipsychotics. Furthermore, it is possible that patients treated with the PP3M LAI antipsychotic had a better prognosis or required less frequent follow-up assessments compared with patients treated with month and 2-week LAIs. Finally, although hospital readmissions is a useful marker of treatment effectiveness, this variable is easily affected by other parameters, such as patient's social and family support, which are unrelated to the medication. Therefore, future studies that will include anxiety, anger and depression measures are required to truly establish the effectiveness of the newest LAIs antipsychotics in BPD.

Conclusion

In summary, to the best of our knowledge, this is the first study comparing the use of oral antipsychotics and their LAIs formulation regarding suicidal behaviour, hospital admissions and concomitant treatments. Despite the limitations of our study, we demonstrated that LAIs were superior in the need of concomitant antipsychotics as well as in the visits to emergency departments compared with oral antipsychotics. Among the LAIs, PP3M showed better treatment outcomes but this finding should be confirmed with larger sample studies. Altogether, our results suggest that the use of LAIs may play a role in the management of BPD. Future research is required to stablish the effectiveness of LAIs in BPD; however, our findings could be useful for clinicians and their practice.

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Conflicts of interest

There are no conflicts of interest.

References

Aguglia A, Serafini G, Nebbia J, Salvi V, Martinotti G, Corbo M, *et al.* (2019). Off-label use of second-generation antipsychotics in borderline personality disorder: a survey of Italian psychiatrists. *J Pers Disord* **445**:33.

American Psychiatric Association Practice Guidelines. (2001). Practice guideline for the treatment of patients with borderline personality disorder. *Am J Psychiatry* **158**: 1–52.

American Psychiatric Association. (2013). Diagnostic and statistical manual of mental disorders. 5th ed. Washington DC: APA Press.

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Bellino S, Bozzatello P, Rinaldi C, Bogetto F (2011). Paliperidone ER in the treatment of borderline personality disorder: a Pilot Study of efficacy and tolerability. *Depress Res Treat* **2011**:680194.

Bogenschutz MP, George Nurnberg H (2004). Olanzapine versus placebo in the treatment of borderline personality disorder. *J Clin Psychiatry* **65**:104–109.

Bozzatello P, Rocca P, Uscinska M, Bellino S (2017). Efficacy and tolerability of asenapine compared with olanzapine in borderline personality disorder: an open-label randomized controlled trial. *CNS Drugs* **31**:809–819.

Carrasco JL, Palomares N, Marsá MD (2012). Effectiveness and tolerability of long-acting intramuscular risperidone as adjuvant treatment in refractory borderline personality disorder. *Psychopharmacology (Berl)* **224**:347–348.

Crawford MJ, Kakad S, Rendel C, Mansour NA, Crugel M, Liu KW, *et al*. (2011). Medication prescribed to people with personality disorder: the influence of patient factors and treatment setting. *Acta Psychiatr Scand* **124**:396–402.

D'Agostino A, Rossi Monti M, Starcevic V (2019). Psychotic symptoms in borderline personality disorder: an update. *Curr Opin Psychiatry* **32**:22–26.

Díaz-Marsá M, Galian M, Montes A, Fernández R, Arza R, López-Ibor J, Carrasco J (2008). Long-acting injectable risperidone in treatment resistant borderline personality disorder. A small series report. *Actas Esp Psiquiatr* **36**:70–74.

Dubovsky AN, Kiefer MM (2014). Borderline personality disorder in the primary care setting. *Med Clin North Am* **98**:1049–1064.

Fang SC, Liao DL, Huang CY, Hsu CC, Cheng SL, Shao YJ (2020). The effectiveness of long-acting injectable antipsychotics versus oral antipsychotics in the maintenance treatment of outpatients with chronic schizophrenia. *Hum Psychopharmacol* **35**:e2729.

Friedel RO, Jackson WT, Huston CS, May RS, Kirby NL, Stoves A (2008). Risperidone treatment of borderline personality disorder assessed by a borderline personality disorder-specific outcome measure: a pilot study. *J Clin Psychopharmacol* **28**:345–347.

García-Carmona JA, Simal-Aguado J, Campos-Navarro MP, Valdivia-Muñoz F, Galindo-Tovar A (2020). Long-acting injectable antipsychotics: analysis of prescription patterns and patient characteristics in mental health from a Spanish Real-World Study. *Clin Drug Investig* **40**:459–468.

Grant BF, Chou SP, Goldstein RB, Huang B, Stinson FS, Saha TD, *et al*. (2008). Prevalence, correlates, disability, and comorbidity of DSM-IV borderline personality disorder: results from the Wave 2 national epidemiologic survey on alcohol and related conditions. *J Clin Psychiatry* **69**:533–545.

Huang Y, Kotov R, de Girolamo G, Preti A, Angermeyer M, Benjet C, *et al*. (2009). DSM-IV personality disorders in the WHO World Mental Health Surveys. *Br J Psychiatry* **195**:46–53.

Leichsenring F, Leibing E, Kruse J, New AS, Leweke F (2011). Borderline personality disorder. *Lancet* **377**:74–84.

Lis S, Bohus M (2013). Social interaction in borderline personality disorder. *Curr Psychiatry Rep* **15**:338.

Martínez-Andrés JA, García-Carmona JA (2019). Clozapine, a controversial gold standard antipsychotic for the 21st century: Switching to paliperidone palmitate 3-monthly improves the metabolic profile and lowers antipsychotic dose equivalents in a treatment-resistant schizophrenia cohort. *Schizophr Res* **212**:234–236.

Martín-Blanco A, Ancochea A, Soler J, Elices M, Carmona C, Pascual JC (2017). Changes over the last 15 years in the psychopharmacological management of persons with borderline personality disorder. *Acta Psychiatr Scand* **136**:323–331.

Montgomery SA, Montgomery D (1982). Pharmacological prevention of suicidal behaviour. *J Affect Disord* **4**:291–298.

Nickel MK, Loew TH, Pedrosa Gil F (2007). Aripiprazole in treatment of borderline patients, part II: an 18-month follow-up. *Psychopharmacology (Berl)* **191**:1023–1026.

Nickel MK, Muehlbacher M, Nickel C, Kettler C, Pedrosa Gil F, Bachler E, *et al*. (2006). Aripiprazole in the treatment of patients with borderline personality disorder: a double-blind, placebo-controlled study. *Am J Psychiatry* **163**:833–838.

Palomares N, Montes A, Díaz-Marsá M, Carrasco JL (2015). Effectiveness of long-acting paliperidone palmitate in borderline personality disorder. *Int Clin Psychopharmacol* **30**:338–341.

Paris J (2015). Why patients with severe personality disorders are overmedicated. *J Clin Psychiatry* **76**:e521.

Pascual JC, Soler J, Puigdemont D, Pérez-Egea R, Tiana T, Alvarez E, Pérez V (2008). Ziprasidone in the treatment of borderline personality disorder: a double-blind, placebo-controlled, randomized study. *J Clin Psychiatry* **69**:603–608.

Rocca P, Marchiaro L, Cocuzza E, Bogetto F (2002). Treatment of borderline personality disorder with risperidone. *J Clin Psychiatry* **63**:241–244.

Rohde C, Polcwiartek C, Correll CU, Nielsen J (2018). Real-world effectiveness of clozapine for borderline personality disorder: results from a 2-year Mirror-Image Study. *J Pers Disord* **32**:823–837.

Samuels J, Eaton WW, Bienvenu OJ 3rd, Brown CH, Costa PT Jr, Nestadt G (2002). Prevalence and correlates of personality disorders in a community sample. *Br J Psychiatry* **180**:536–542.

Shafti SS, Shahveisi B (2010). Olanzapine versus haloperidol in the management of borderline personality disorder: a randomized double-blind trial. *J Clin Psychopharmacol* **30**:44–47.

Shah R, Zanarini MC (2018). Comorbidity of borderline personality disorder: current status and future directions. *Psychiatr Clin North Am* **41**:583–593.

Slotema CW, Blom JD, Niemantsverdriet MBA, Deen M, Sommer IEC (2018). Comorbid diagnosis of psychotic disorders in borderline personality disorder: prevalence and influence on outcome. *Front Psychiatry* **9**:84.

Soloff PH, George A, Nathan RS, Schulz PM, Ulrich RF, Perel JM (1986). Progress in pharmacotherapy of borderline disorders. A double-blind study of amitriptyline, haloperidol, and placebo. *Arch Gen Psychiatry* **43**:691–697.

Soloff PH, George A, Nathan S, Schulz PM, Cornelius JR, Herring J, Perel JM (1989). Amitriptyline versus haloperidol in borderlines: final outcomes and predictors of response. *J Clin Psychopharmacol* **9**:238–246.

Soloff PH, Cornelius J, George A, Nathan S, Perel JM, Ulrich RF (1993). Efficacy of phenelzine and haloperidol in borderline personality disorder. *Arch Gen Psychiatry* **50**:377–385.

Stepp SD, Lazarus SA, Byrd AL (2016). A systematic review of risk factors prospectively associated with borderline personality disorder: taking stock and moving forward. *Personal Disord* **7**:316–323.

Torgersen S, Kringlen E, Cramer V (2001). The prevalence of personality disorders in a community sample. *Arch Gen Psychiatry* **58**:590–596.

Ullrich S, Coid J (2009). The age distribution of self-reported personality disorder traits in a household population. *J Pers Disord* **23**:187–200.

Van Veen M, Wierdsma AI, van Boeijen C, Dekker J, Zoeteman J, Koekkoek B, Mulder C. (2019). Suicide risk, personality disorder and hospital admission after assessment by psychiatric emergency services. *BMC Psychiatry* **19**:157.

Von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP (2008). The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *J Clin Epidemiol* **61**:344–349.

Zanarini MC, Frankenburg FR (2001). Olanzapine treatment of female borderline personality disorder patients: a double-blind, placebo-controlled pilot study. *J Clin Psychiatry* **62**:849–854.

Zanarini MC, Frankenburg FR, Hennen J, Silk KR (2004a). Mental health service utilization by borderline personality disorder patients and Axis II comparison subjects followed prospectively for 6 years. *J Clin Psychiatry* **65**:28–36.

Zanarini MC, Frankenburg FR, Parachini EA (2004b). A preliminary, randomized trial of fluoxetine, olanzapine, and the olanzapine-fluoxetine combination in women with borderline personality disorder. *J Clin Psychiatry* **65**:903–907.

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IV- DISCUSIÓN

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Los fármacos ansiolíticos e hipnóticos son frecuentemente prescritos en los países occidentales. Un estudio realizado por Bachhuber y cols., en EEUU, muestra un aumento del 67% en los adultos que son prescritos con benzodiazepinas, desde los 8.1 millones hasta los 13.5 millones entre los años 1996 a 2013 (225). De hecho, en la última década, la prevalencia del uso de benzodiazepinas en la población general varía del 12.6% en EEUU (226), el 13,8% en Francia (227), entre el 10% y el 25% en los Países Bajos (228), y el 26,1% en el Reino Unido (229). Además, Kirby y cols., (1999); demostraron que el 28,6% de los pacientes diagnosticados de un trastorno mental tomaban benzodiazepinas frente al 15,2% de los pacientes sin ningún trastorno mental (230). En nuestra cohorte, basada en usuarios de la red de Salud Mental, el 68% de los pacientes fueron tratados con benzodiazepinas. En particular, la mayoría de los pacientes tomaron un solo tipo de benzodiazepina (48%), mientras que el 19% utilizaron al menos 2 benzodiazepinas diferentes.

4.1 Factores de riesgo asociados al consumo de benzodiazepinas en Salud Mental

Sexo

El 70% de las mujeres y el 66% de los hombres de nuestra cohorte tomaban benzodiazepinas. Nuestros resultados demuestran que ser "mujer" es un factor de riesgo independiente para el consumo de benzodiazepinas (OR=1.559 *vs.* "hombres", p=0.024). Nuestros resultados están en línea con estudios previos que muestran una mayor proporción de consumo de benzodiazepinas en mujeres que en hombres. Por ejemplo, McHugh y cols., mostraron que el 58% de las mujeres tomaban benzodiazepinas frente al 44% de los hombres (231). El estudio realizado en España por Martínez-Cengotitabengoa y cols., demuestra que las benzodiazepinas son prescritas con mayor frecuencia en mujeres, 47,6%, que en hombres, 36,1% (232), dato que coincide, a su vez, con el estudio realizado en Canadá, por Maclagan y cols., en el que el 17,2% de las mujeres tomaban benzodiazepinas frente al 15,3% de los hombres (233). Algunos estudios en EEUU (234, 3) sugieren que esta mayor prevalencia de consumo de benzodiazepinas en mujeres puede ser consecuencia de que, con mayor

frecuencia, padecen trastornos afectivos o síntomas como ansiedad e insomnio, dolencias tratadas, entre otros psicofármacos, con benzodiazepinas.

Sin embargo, los resultados de este estudio no muestran diferencias estadísticamente significativas entre las dosis diarias equivalentes de diazepam utilizadas entre ambos sexos. En el estudio de Martínez-Cengotitabengoa y cols., las DDD de benzodiazepinas superan en el 70% de los hombres a las DDD estándar, mientras que en las mujeres, esto sucede en el 53,1% (232).

- Trastorno mental

Nuestros resultados muestran que un 67% de los pacientes diagnosticados con un trastorno mental grave tomaba benzodiazepinas. Además, el 81% de los pacientes diagnosticados con un trastorno afectivo tenían prescritos fármacos benzodiazepínicos. Además, nuestros resultados muestran que padecer una un trastorno mental con clínica afectiva es un factor de riesgo independiente para el consumo de benzodiazepinas (OR=1.542 *vs.* no afectivo, p=0.040). Sin embargo, no encontramos una asociación significativa entre el consumo de benzodiazepinas y la gravedad del trastorno mental.

Según el estudio de Campanha y cols., realizado en Brasil, sí que existen diferencias estadísticamente significativas en el uso de benzodiazepinas entre pacientes con diferentes enfermedades mentales, con trastorno bipolar, trastorno del ánimo y trastorno de ansiedad, el uso de fármacos benzodiazepínicos estaba presente, respectivamente, en el 23,3%, 14,7% y 8,1% de las personas con dichos trastornos (235).

- Drogas de abuso

La prevalencia de fumadores y personas que tomaban drogas en nuestra cohorte es de un 44% y 33%, respectivamente. Una proporción similar de consumidores de drogas, fue encontrada en los pacientes diagnosticados de esquizofrenia (35%) y de trastorno limite de personalidad (30%). Estos resultados son similares a los mostrados por estudios previos que muestran una prevalencia de consumo de drogas en el 27,5% de pacientes diagnosticados de esquizofrenia (236) y de entre un 27-38% de los pacientes diagnosticados de trastorno limite de personalidad (237, 238). Además, nuestros resultados muestran que consumir drogas de abuso, como alcohol, cannabis y

cocaína, es un factor de riesgo independiente para el consumo de benzodiazepinas (OR=1.671 *vs.* pacientes no toman drogas, p=0.011). En conjunto, nuestros resultados son similares a un estudio previo en una población danesa, realizado por Toftdahl y cols., en el que se muestra que el 32% de los pacientes con trastorno bipolar consumen drogas de abuso, dentro de ellas el alcohol es el más utilizado (38,9%), seguido por el cannabis (5,6%) y la cocaína (5,6%) (239). Además, un estudio realizado en EEUU mostró que las personas que tomaban drogas de abuso, consumían entre 3,5 y 24 veces más dosis de benzodiazepinas que la población general (240).

- Tratamiento antipsicótico utilizado

El 86% de los pacientes del estudio que no eran tratados con LAIs tenía prescrita alguna benzodiazepina. En contraste, el 62% de los pacientes tratados con LAIs era además tratado con benzodiazepinas. Nuestros resultados muestran que el tratamiento con LAIs está asociado de forma independiente con un menor consumo de benzodiazepinas (OR=5.226 *vs.* no LAIs, p=0.001). Sin embargo, un estudio realizado entre 2006 y 2009 con pacientes tratados con olanzapina oral e inyectable de la larga duración concluye que no existen diferencias signigicativas en la prevalencia de uso de benzodiazepinas, el 39% en el grupo de olanzapina inyectable frente al 37,3% de los pacientes con olanzapina oral (241).

4.2 Patrones de prescripción y consumo de benzodiazepinas en enfermedades mentales

- Uso de benzodiazepinas diferenciadas por sexo y trastorno mental

Clonazepam fue la benzodiazepina más utilizada por los pacientes del estudio (33% mujeres y 32% hombres), seguida por lorazepam (32% mujeres y 24% hombres) y, en tercer lugar, diazepam (21% mujeres y 22% hombres). De forma paralela, tanto clonazepam (24,21%) como lorazepam (20,64%) fueron las benzodiazepnas más prescritas para los diferentes trastornos mentales. Sin embargo, es necesario puntualizar que clonazepam es más prevalente en trastornos no afectivos mientras que lorazepam lo es en trastornos afectivos. Acorde a nuestros resultados, Naloto y cols., mostraron que el clonazepam es la benzodiazepina más utilizada, entre la población brasileña con algún trastorno mental que consume benzodiazepinas, con un 52,1% (242). Otro estudio realizado en España muestra que lorazepam es el anisolítico más utilizado, con una DDD: 1000 hab/día de 20,5 (243). Por el contrario, otros estudios muestran que diazepam (244, 245) o bromazepam (246) son las benzodiazepinas más utilizadas dentro de la población anciana de Sao Paulo y los consumidores de

benzodiazepinas de la región de Ribeirao en Brasil. Estas diferencias pueden deberse a los diferentes grupos de pacientes estudiados, por las diferentes benzodiazepinas autorizadas en cada país o por diferentes hábitos de prescripción médica.

Además, nuestro estudio muestra que el uso de benzodiazepinas es mayor y más prolongado al recomendado en más de un 48% de los pacientes. De forma similar, un estudio realizado en población francesa el 75,9% de los pacientes utilizaba benzodiazepinas durante más de seis meses (247). Las guías de práctica clínica y la evidencia científica recomiendan el uso de benzodiazepinas como tratamiento adyuvante en ansiedad, insomnio y depresión durante las primeras cuatro semanas del tratamiento. Tal y como señalan Smith y Tett (248), las guías clínicas y las campañas sanitarias contribuyen a concienciar sobre el uso inadecuado de las benzodiazepinas. Sin embargo, en los países occidentales los pacientes no son tratados en concordancia con las guías clínicas basadas en la evidencia científica (234). Está demostrado que el uso prolongado, durante más de un año, de benzodiazepinas aumenta el riesgo de sufrir síndrome de abstinencia, accidentes, intentos de suicidio (especialmente en pacientes depresivos), además de reducir la capacidad de trabajar y de incrementarse el coste económico por hospitalizaciones (227, 228, 229).

- Dosis diarias equivalentes de diazepam

La dosis media diaria equivalente de diazepam en nuestra cohorte es de 24,9 mg (24,90 ±1,42). No existen diferencias estadísticamente significativas entre mujeres y hombres (27,41±2,04 y 23,29±1,79, respectivamente). Un estudio realizado en Australia entre 2013 y 2016, muestra que la media de DDD/1000 hab/día de benzodiazepina es de 14,2, siendo mayor en mujeres que en hombres (249). De la misma manera, un estudio canadiense, realizado entre 2011 y 2013, presenta una DDD/1000hab/día de benzodiazepinas media de 24,93, puntualizando también que las mujeres toman mayor cantidad de benzodiazepinas (250). En Uruguay, entre los años 2010 y 2012, la DDD/1000 hab/día alcanzó 73,76 (251). Y en España 82,9 DDD/1000hab/día (243).

Sin embargo, sí existen diferencias estadísticamente significativas (p=0.001) entre pacientes diagnosticados de trastornos afectivos (40,35±3,36) y no afectivos (21,98±1,37).

Además, nuestros resultados mostraron que aquellos pacientes tratados con un LAI tomaban una dosis equivalente de diazepam significativamente menor (17,50 ± 1,39, p=0.001) que aquellos que no eran tratados con LAIs (40,25 ± 2,99). En un estudio realizado en Alemania, en 2003 y 2004, con una cohorte de pacientes con esquizofrenia,

se observó que los pacientes que fueron tratados con olanzapina (el 6,9% de ellos utilizaban LAIs), utilizaron una menor dosis acumulada de diazepam en 5 días que el resto de pacientes que no utilizan la olanzapina (77,9 mg *vs.* 89 mg, respectivamente) (252). Por otro lado, la revisión sistemática realizada por Sampson y cols., en 2016, no encuentra diferencias estadísticamente significativas en la dosis de benzodiazepinas administrada a pacientes diagnosticados de esquizofrenia que tomaban risperidona oral o risperidona inyectable (253).

- Tratamiento concomitante

Los fármacos antipsicóticos se utilizaban en el 100% de los pacientes con esquizofrenia y en el 95% con psicosis. También en el 66% de los pacientes con trastorno de personalidad, el 61% con trastorno bipolar y el 67% con trastorno esquizoafectivo. En el estudio, el 67% de los enfermos con esquizofrenia estaban tratados con, al menos, dos antipsicóticos diferentes. Además, el uso de fármacos antidepresivos era generalizado en el 100% de los pacientes con depresión, en el 64% con trastorno ansioso-depresivo y en el 49% de aquellas personas con trastorno de personalidad. Los estabilizadores del ánimo eran utilizados por el 74% y el 48% de los pacientes con trastornos bipolar y esquizoafectivo, respectivamente. En el estudio de Baldessarini y cols., sobre una población estadounidense con trastorno bipolar, el 70% de los pacientes seguían tratamientos con varias clases de fármacos (254). Al igual que el estudio de Lang y cols., que muestra que el 68,6% de los pacientes estadounidenses con trastorno bipolar utilizaban fármacos antipsicóticos, combinados con fármacos anticonvulsivantes o estabilizadores del ánimo (255).

Por otro lado, en un meta-análisis realizado en Corea en pacientes con esquizofrenia, el 17,8% utilizaban dos antipsicóticos, mientras que solo el 0,2% utilizaban tres o más antipsicóticos (256). Siguiendo la tendencia anterior, un estudio con datos globales entre 1970 y 2009, muestra que el 19,2% de las personas con esquizofrenia utilizaban dos antipsicóticos, mientras que el 1,2% utilizaban tres (257).

4.3 Impacto de LAIs en el uso de benzodiazepinas en Salud Mental

En nuestra cohorte, el uso de LAIs como monoterapia fue aproximadamente del 14%. Los fármacos más utilizados como tratamiento coadyuvante, en los pacientes de la muestra, fueron las benzodiazepinas, seguidas por los antipsicóticos y por último, el biperideno. Nuestros resultados muestran diferencias estadísticamente significativas en las dosis de benzodiazepinas, expresadas en equivalentes de diazepam, que tomaban los pacientes que utilizaban diferentes LAIs: palmitato de paliperidona

mensual (PP1M) y palmitato de paliperidona trimestral (PP3M) (12,5 y 7,8 mg respectivamente) comparado con aripiprazol mensual (26,1 mg) y LAIs bisemanales (37,2 mg). Además, los pacientes tratados con PP1M y PP3M utilizaban menores dosis diarias equivalentes de haloperidol, (3,2 y 3,1 mg respectivamente), comparado con pacientes tratados con formulaciones bisemanales (6,90 mg).

En cuanto a la distribución por sexo de los LAIs, encontramos que la formulación mensual de aripiprazol se encontraba distribuida similarmente entre ambos sexos, mientras que el resto de formulaciones de LAIs se utilizaban principalmente en hombres. Una posible explicación es que la paliperidona se utiliza en pacientes con esquizofrenia y otros trastornos mentales que presentan mayores niveles de hostilidad (258), síntoma que es más común en hombres. No hay datos que justifiquen la utilización de la formulación de aripiprazol mensual para el manejo de la agresividad a largo plazo (259). Sin embargo, el uso de la formulación mensual de aripiprazol en mujeres produce menos efectos adversos, ganancia de peso (260), aumento de niveles de prolactina y amenorrea (261) o efectos extrapiramidales (262), que con otros antipsicóticos.

Además, nuestros resultados muestran que los pacientes que eran tratados con LAIs son mayores y con mayor número de años de evolución de la enfermedad. Esto podría indicar que los clínicos o los pacientes prefieren iniciar tratamientos orales pero más tarde, por incumplimiento o por otros factores, cambiar a LAIs. En este sentido, la evidencia más reciente sugiere que el tratamiento con LAIs desde el primer episodio de psicosis presenta mejores resultados clínicos y mejor pronóstico a medio plazo frente al tratamiento oral (263).

4.4 Impacto de los LAIs en el uso de benzodiazepinas en pacientes diagnosticados de esquizofrenia y trastorno de personalidad límite

En nuestra cohorte, el 84% de los pacientes con esquizofrenia fueron tratados, además del antipsicótico principal, con al menos otro antipsicótico, mientras que el 16% eran tradados con otros dos antipsicóticos orales. Además, aproximadamente un 50% de los pacientes diagnosticados de esquizofrenia fueron tratados con benzodiazepinas. Estas ratios son más altas que las mostradas en otros estudios en los que un 40-49% de los pacientes son tratados con, al menos, dos antipsicóticos (264, 265). Sin embargo, los resultados de nuestro estudio están en línea con estudios previos que muestran el 25-79% de pacientes diagnositicados de esquizofrenia son tratados con benzodiazepinas (264, 266, 265). Un estudio internacional realizado en 25 paises muestra que el 37,4% de los diagnosticados de esquizofrenia o trastorno esquizoafectivo que eran tratados con olanzapina-LAI, utilizaban benzodiazepinas como tratamiento concomitante (267). Finalmente, un 24% de nuestros pacientes fueron tratados con otros psicofármacos como antidepresivos y anticolinérgicos, proporción

similar a la mostrada en estudios previos: el 13-30% con antidepresivos (264, 266, 265) y un 11-17% con estabilizadores del ánimo (264, 265, 268).

Respecto a la necesidad de utilizar otros psicofármacos en los pacientes tratados con LAIs, nuestros resultados muestran que los pacientes diagnosticos de esquizofrenia y tratados con PP1M y PP3M utilizaban menos benzodiazepinas respecto a otros pacientes que eran tratados con aripiprazol mensual y LAIs bisemanales. A pesar de que para el tratamiento de primera línea de los síntomas psicóticos se utilizan antipsicóticos una reciente revisión sistemática concluye que el tratamiento de la esquizofrenia con benzodiazepinas y antipsicóticos es más eficaz que el tratamiento con monoterapia antipsicótica (269). Además de tratar síntomas psicóticos, las benzodiazepinas se prescriben a pacientes con enfermedades psicóticas para mejorar la hipnosis y disminuir la agresividad (270). Algunos estudios han demostrado que la paliperidona presenta una mayor eficacia (aunque no significativa) en el manejo de síntomas psicóticos, como la agresividad, comparada con el aripiprazol mensual y los LAIs bisemanales (271, 272). Además, aripiprazol ha sido relacionado con producir mayor riesgo de acatisia (273), comparado con otros antipsicóticos, síntoma que puede tratarse con benzodiazepinas (274).

Por otra parte, nuestros resultados mostraron que el uso de LAIs mensuales y trimestrales se acompañó de un menor uso concomitante de otros antipsicóticos comparados con formulaciones bisemanales. Los resultados del estudio no están en consonancia con datos previos que muestran que la utilización de LAIs de segunda generación está asociada con un aumento del uso de antipsicóticos orales (275). Esta discrepancia puede originarse por diferencias en los tratamientos estudiados, ya que, en el estudio anteriormente citado, la risperidona es el LAI más prevalente en el grupo de los LAIs de segunda generación, mientras que en nuestro estudio se incluye en el grupo de LAIs bisemanales. Sin embargo, el presente estudio está en línea con un estudio previo que muestra que PP1M está asociado con un menor uso concomitante de antipsicóticos orales (58,8%) comparado con otros LAIs como risperidona (88,9%) y de flufenazina (80%) (276). De fotma similar, el estudio de Aggarwal y cols., no muestra diferencias en el uso de antipsicóticos orales concomitantes cuando comparan LAIs bisemanales de risperidona, flufenazina o haloperidol (277). El menor uso de antipsicóticos orales en el grupo de pacientets tratados con PP1M y PP3M es posible que sea debido al gran conocimiento y confianza que los prescriptores tienen en estos LAIs. Otra explicación podría ser que los médicos no confíen en el compromiso de adherencia del paciente al tratamiento oral y prefieren prescribir fármacos de acción mensual o trimestral.

En pacientes con trastorno de personalidad límite, el uso de PP1M y PP3M reducía el uso diario de benzodiazepinas, comparados con pacientes que utilizaban LAI mensual de aripiprazol o LAIs de risperidona, sin diferencias entre grupos en el uso de antidepresivos, estabilizadores del ánimo y biperideno.

La dosis equivalente diaria de diazepam en pacientes con trastorno de personalidad límite fue de 40,55 mg/día, mientras que la dosis diaria equivalente de haloperidol fue de 5,92 mg/día y la dosis diaria de biperideno fue de 0,26 mg/día. Además nuestros resultados mostraron que los pacientes tratados con LAIs tomaban menores dosis diarias equivalentes de diazepam, comparados con pacientes tratados con antipsicóticos orales (16,78 y 58,55 mg, respectivamente). Además, los pacientes tratados con PP3M asociaban una menor dosis diaria de diazepam (3,33 mg), respecto a pacientes tratados aripiprazol-LAI (30,29 mg) y risperidona-LAI (22,40 mg). Nuestros resultados están en línea con estudios previos, como el publicado por Palomares y cols. (278), donde se demuestra que el uso concomitante de antipsicóticos y benzodiazepinas se reduce del 56% al 25% y del 81% al 56%, respectivamente, en pacientes con trastorno de personalidad límite que sustituyen el tratamiento con paliperidona oral a PP1M. Además, nuestros resultados muestran que más de un 50% de pacientes utilizaban una combinación de benzodiazepinas, antipsicóticos y antidepresivos y un 25% tomaban fármacos estabilizadores del ánimo. Estos resultados están en línea con los presentados en otros estudios en los que entre un 40- 50% de los pacientes con trastorno límite de personalidad utilizan al menos tres psicofármacos de familias diferentes (279, 237, 280).

Un estudio observacional de 20 años de duración muestra como los estos pacientes son tratados en polifarmacia pero que la frecuencia de prescripciones de benzodiazepines se ha reducido de un 77% en el año 2001 a un 23% en 2021 (281). No obstante, un reciente meta-análisis (282) muestra que la eficacia de los psicofármacos en el tratamiento del trastorno de personalidad límite es limitada, mostrando que los antipsicóticos de segunda generación, estabilizadores del ánimo y antidepresivos no reducen la severidad de este trastorno sino que, con baja evidencia, los estabilizadores del ánimo podrían mejorar algunos síntomas como agresividad, irrtabilidad y labilidad emocional mientras que los antipsicóticos de segunda generación podrían mejorar, de forma general, los síntomas psiquiátricos.

V- CONCLUSIONES

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- Las benzodiazepinas son un grupo de fármacos prescritos en >65% de los pacientes de Salud Mental en nuestra cohorte.
- Las benzodiazepinas más prescritas son clonazepam, lorazepam y diazepam.
- La mayoría de los pacientes utilizaba una benzodiazepina.
- La dosis media diaria de benzodiazepinas utilizada equivalía a 25 mg de diazepam.
- Las benzodiazepinas eran prescritas con mayor asiduidad de la deseada y a mayores dosis.
- La utilización de LAIs en pacientes con esquizofrenia redujo la necesidad de utilizar benzodiazepinas como medicación concomitante, así como de su dosis media diaria administrada.
- Los LAIs pueden tener un papel en el tratamiento del trastorno de personalidad límite.
- Entre LAIs, la presentación trimestral de paliperidona fue la que presentó mejores resultados en el tratamiento de estos pacientes, aunque son necesarios más estudios que confirmen este resultado.
- Son necesarios más estudios que investiguen el uso de benzodiazepinas y LAIs en pacientes con enfermedades mentales.

VI- REFERENCIAS BIBLIOGRÁFICAS

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1. Sternbach LH. The discovery of librium. Agents Actions. 1972 Jun;2(4):193-6.

2. Wick JY. The History of Benzodiazepines. The Consultant Pharmacist. 2013 Sep 1;28(9):538–48.

3. Jacob TC, Moss SJ, Jurd R. $GABA_A$ receptor trafficking and its role in the dynamic modulation of neuronal inhibition. Nat Rev Neurosci. 2008 May;9(5):331–43.

4. Ashton H. Toxicity and adverse consequences of benzodiazepine use. Psychiatric Annals. 1995;25:158-65.1.

5. Díaz García Ó, Dévora Figueroa C, Díez González LM, Fernández del Pozo de Salamanca MB. Farmacología del sistema nervioso. En: Trastornos neurológicos y neuropsiquiátricos. Madrid: Consejo General de Colegios Oficiales de Farmacéuticos; 2019.p.1-120.

6. Sieghart W, Fuchs K, Tretter V, Ebert V, Jechlinger M, Höger H, et al. Structure and subunit composition of $GABA_A$ receptors. Neurochemistry International. 1999 May;34(5):379–85.

7. Macdonald RL, Olsen RW. $GABA_A$ receptor channels. Annu Rev Neurosci 1994;17:569-602.

8. McKernan RM, Whiting PJ. Which $GABA_A$-receptor subtypes really occur in the brain? Trends in Neurosciences. 1996 Apr 1;19(4):139–43.

9. Simon J, Wakimoto H, Fujita N, Lalande M, Barnard EA. Analysis of the set of $GABA_A$ receptor genes in the human genome. Journal of Biological Chemistry. 2004 Oct;279(40):41422–35.

10. Low K, Crestani F, Keist R, Benke D, Brünig I, Benson JA et al. Molecular and Neuronal Substrate for the Selective Attenuation of Anxiety. Science. 2000 Oct 6;290(5489):131–4.

11. Rudolph U, Crestani F, Benke D, Brünig I, Benson JA, Fritschy JM et al. Benzodiazepine actions mediatel by pecific γ-aminobutyric acid$_A$ receptor subtypes. Nature 1999;401:796-800.

12. Gravielle MC. Activation-induced regulation of GABAA receptors: Is there a link with the molecular basis of benzodiazepine tolerance? Pharmacological Research. 2016 Jul;109:92–100.

13. Faught E. Pharmacokinetic considerations in prescribing antiepileptic drugs. Epilepsia. 2001;42 Suppl 4:19-23.

14. Manchester KR, Lomas EC, Waters L, Dempsey FC, Maskell PD. The emergence of new psychoactive substance (NPS) benzodiazepines: A review. Drug Test Analysis. 2018 Jan;10(1):37–53.

15. Anderson GD, Miller JW. Benzodiazepines: chemistry, biotransformation, and pharmacokinetics. In: Levy RH, Mattson RH, Meldrum BS, Peracca E, eds. Antiepileptic drugs. 5th edn. Philadelphia PA: Lippincott Williams & Wilkins. 2002:187-205.

16. Griffin CE, Kaye AM, Bueno FR, Kaye AD, Kaye AD. Benzodiazepine Pharmacology and Central Nervous System-Mediated Effects. Ochsner J 2013;13:214–23.

17. Veldhorst-Janssen NML, Fiddelers AAA, van der Kuy P-HM, Neef C, Marcus MAE. A review of the clinical pharmacokinetics of opioids, benzodiazepines, and antimigraine drugs delivered intranasally. Clinical Therapeutics. 2009 Dec;31(12):2954–87.

18. Rey E, Tréluyer J-M, Pons G. Pharmacokinetic Optimisation of Benzodiazepine Therapy for Acute Seizures: Focus on Delivery Routes. Clinical Pharmacokinetics. 1999 Jun;36(6):409–24.

19. Shyken JM, Babbar S, Babbar S, Forinash A. Benzodiazepines in Pregnancy. Clinical Obstetrics & Gynecology. 2019 Mar;62(1):156–67.

20. McElhatton PR. The effects of benzodiazepine use during pregnancy and lactation. Reproductive Toxicology. 1994 Nov;8(6):461–75.

21. Soyka M. Treatment of Benzodiazepine Dependence. Longo DL, editor. N Engl J Med. 2017 Mar 23;376(12):1147–57.

22. Díaz Gutiérrez MJ. Sobredosificación de benzodiazepinas en ancianos y caídas: implicaciones clínicas y económicas. Universidad del País Vasco; 2019.

23. Manchikanti L, Christo PJ, Trescot A, Falco FJE, American Society of Interventional Pain Physicians. Pain medicine & interventional pain management: a comprehensive review: clinical aspects. n.d.

24. Greenblatt D, Shader R, Divoll M, Harmatz J. Benzodiazepines: a summary of pharmacokinetic properties. British Journal of Clinical Pharmacology. 1981 Feb;11(S1):11S-16S.

25. Brayfield A (ed): Martindale: The Complete Drug Reference, ed 38. London, Pharmaceutical Press, 2014.

26. Trevor AJ. Chapter 22: sedative–hypnotic drugs. In: Katzung BG, Trevor AJ, editors. Basic and clinical pharmacology, 13e. New York: McGraw-Hill Medical; 2015.

27. Ralvenius WT, Benke D, Acuña MA, Rudolph U, Zeilhofer HU. Analgesia and unwanted benzodiazepine effects in point-mutated mice expressing only one benzodiazepine-sensitive GABAA receptor subtype. Nat Commun. 2015 Apr;6(1):6803.

28. Rudolph U, Möhler H. GABAA Receptor Subtypes: Therapeutic Potential in Down Syndrome, Affective Disorders, Schizophrenia, and Autism. Annu Rev Pharmacol Toxicol. 2014 Jan 6;54(1):483–507.

29. Shader RI, Greenblatt DJ. Benzodiazepines: some aspects of their clinical pharmacology. Ciba Found Symp. 1979;74:141–55.

30. International Narcotics Control Board. Psychotropic Substances 2006. [Internet] Available from: http://www.incb.org/pdf/e/tr/psy/2006/psychotropic_substances_2006.pdf.

31. Riss J, Cloyd J, Gates J, Collins S. Benzodiazepines in epilepsy: pharmacology and pharmacokinetics. Acta Neurologica Scandinavica. 2008 Aug;118(2):69–86.

32. Horowski R. Dependence liability of lormetazepam: are all benzodiazepines equal? The case of the new i.v. lormetazepam for anesthetic procedures. J Neural Transm. 2020 Aug;127(8):1107–15.

33. Lam RW, Kennedy SH, Grigoriadis S, McIntyre RS, Milev R, Ramasubbu R, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) Clinical guidelines for the management of major depressive disorder in adults. Journal of Affective Disorders. 2009 Oct;117:S26–43.

34. Bandelow B, Michaelis S, Wedekind D. Treatment of anxiety disorders. Dialogues in Clincal Neuroscience. 2017 Jun;19(2):93-107.

35. Breilmann J, Girlanda F, Guaiana G, Barbui C, Cipriani A, Castellazzi M, et al. Benzodiazepines versus placebo for panic disorder in adults. Cochrane Common Mental Disorders Group, editor. Cochrane Database of Systematic Reviews. 2019 Mar 28.

36. Sawada N, Uchida H, Suzuki T, Watanabe K, Kikuchi T, Handa T, et al. Persistence and compliance to antidepressant treatment in patients with depression: A chart review. BMC Psychiatry. 2009 Jun;9(1):38.

37. Pfeiffer PN, Ganoczy D, Zivin K, Valenstein M. Benzodiazepines and Adequacy of Initial Antidepressant Treatment for Depression. Journal of Clinical Psychopharmacology. 2011 Jun;31(3):360–4.

38. Chouinard G: Issues in the clinical use of benzodiazepines: potency, withdrawal, and rebound. J Clin Psychiatry. 2004;65Suppl5:7-12.

39. Buffett-Jerrott SE, Stewart SH. Cognitive and sedative effects of benzodiazepine use. Curr Pharm Des. 2002;8(1):45-58.

40. Lader M, Tylee A, Donoghue J. Withdrawing Benzodiazepines in Primary Care: CNS Drugs. 2009;23(1):19–34.

41. Mura T, Proust-Lima C, Akbaraly T, Amieva H, Tzourio C, Chevassus H, Picot MC, Jacqumin-Gadda H, Berr C. Chronic use of benzodiazepines and latent cognitive decline in the elderly: results from the Three-city study. European Neuropsychopharmacology. 2013 Mar;23(3):212-23.

42. Pariente A, de Gage SB, Moore N, Bégaud B. The Benzodiazepine–Dementia Disorders Link: Current State of Knowledge. CNS Drugs. 2016 Jan;30(1):1–7.

43. Rizvi SJ, Sproule BA, Gallaugher L, McIntyre RS, Kennedy SH. Correlates of benzodiazepine use in major depressive disorder: The effect of anhedonia. Journal of Affective Disorders. 2015 Nov;187:101–5.

44. Demaagd G. High-risk drugs in the elderly population. Geriatric Nursing. 1995 Sep;16(5):198–207.

45. Pariente A, Dartigues J-F, Benichou J, Letenneur L, Moore N, Fourrier-Réglat A. Benzodiazepines and Injurious Falls in Community Dwelling Elders: Drugs & Aging. 2008;25(1):61–70.

46. Brandt J, Leong C. Benzodiazepines and Z-Drugs: An Updated Review of Major Adverse Outcomes Reported on in Epidemiologic Research. Drugs R D. 2017 Dec;17(4):493–507.

47. Greenblatt DJ, Sellers EM, Shader RI. Drug therapy: drug disposition in old age. N Engl J Med. 1982 May 6;306(18):1081-8.

48. Montamat SC, Cusack BJ, Vestal RE. Management of drug therapy in the elderly. N Engl J Med. 1989 Aug 3;321(5):303-9.

49. Paterniti S, Dufouil C, Alpérovitch A. Long-Term Benzodiazepine Use and Cognitive Decline in the Elderly: The Epidemiology of Vascular Aging Study: Journal of Clinical Psychopharmacology. 2002 Jun;22(3):285–93.

50. Wikner BN, Stiller C-O, Bergman U, Asker C, Källén B. Use of benzodiazepines and benzodiazepine receptor agonists during pregnancy: neonatal outcome and congenital malformations. Pharmacoepidem Drug Safe. 2007 Nov;16(11):1203–10.

51. Hood SD, Norman A, Hince DA, Melichar JK, Hulse GK. Benzodiazepine dependence and its treatment with low dose flumazenil: Benzodiazepine dependence and its treatment. Br J Clin Pharmacol. 2014 Feb;77(2):285–94.

52. Rickels K, Schweizer E, Case WG, Greenblatt DJ. Long-term Therapeutic Use of Benzodiazepines: I. Effects of Abrupt Discontinuation. Archives of General Psychiatry. 1990 Oct 1;47(10):899–907.

53. Busto U, Sellers EM, Naranjo CA, Cappell H, Sanchez-Craig M, Sykora K. Withdrawal Reaction after Long-Term Therapeutic Use of Benzodiazepines. N Engl J Med. 1986 Oct 2;315(14):854–9.

54. Ashton H. Benzodiazepine abuse. In: Caan W, de Belleroche J, eds. Drink, drugs and dependence: from science to clinical practice. London: Routledge, 2002:197-212.

55. Soyka M, Steinberg R, Vollmer M. Entzugsphänomene bei schrittweisem Benzodiazepinentzug [Withdrawal phenomena in stepwise withdrawal of benzodiazepines]. Nervenarzt. 1988 Dec;59(12):744-8.

56. Lader M, Kyriacou A. Withdrawing Benzodiazepines in Patients With Anxiety Disorders. Curr Psychiatry Rep. 2016 Jan;18(1):8.

57. Soyka M, Batra A. Benzodiazepin-Abhängigkeit. In: Vorderholzer U, Hohagen. F, eds. Therapie psychischer Erkrankungen State of the Art. Munich, Germany: Urban and Fischer, 2014:55-62.

58. De las Cuevas C, Sanz E, de la Fuente J. Benzodiazepines: more 'behavioural' addiction than dependence. Psychopharmacology. 2003 May;167(3):297–303.

59. Ashton H. The diagnosis and management of benzodiazepine dependence. Current Opinion in Psychiatry. 2005 May;18(3):249–55.

60. Uzun S, Kozumplik O, Mimica N, Folnegović-Šmalc V. Nuspojave psihofarmaka. 2005.

61. O'brien CP. Benzodiazepine use, abuse, and dependence. J Clin Psychiatry. 2005;66 Suppl 2:28-33.

62. Licata SC, Rowlett JK. Abuse and dependence liability of benzodiazepine-type drugs: GABAA receptor modulation and beyond. Pharmacology Biochemistry and Behavior. 2008 Jul;90(1):74–89.

63. Okumura Y, Shimizu S, Matsumoto T. Prevalence, prescribed quantities, and trajectory of multiple prescriber episodes for benzodiazepines: A 2-year cohort study. Drug and Alcohol Dependence. 2016 Jan;158:118–25.

64. Lim B, Sproule BA, Zahra Z, Sunderji N, Kennedy SH, Rizvi SJ. Understanding the effects of chronic benzodiazepine use in depression: a focus on neuropharmacology. International Clinical Psychopharmacology. 2020 Sep;35(5):243–53.

65. Gerak LR. Selective changes in sensitivity to benzodiazepines, and not other positive GABAA modulators, in rats receiving flunitrazepam chronically. Psychopharmacology. 2009 Jul;204(4):667–77.

66. Vinkers CH, Olivier B. Mechanisms Underlying Tolerance after Long-Term Benzodiazepine Use: A Future for Subtype-Selective Receptor Modulators? Advances in Pharmacological Sciences. 2012;2012:1–19.

67. Gutiérrez ML, Ferreri MC, Farb DH, Gravielle MC. GABA-induced uncoupling of GABA/benzodiazepine site interactions is associated with increased phosphorylation of the GABA A receptor: GABA-Induced Phosphorylation of GABA A Receptors. Journal of Neuroscience Research. 2014 Aug;92(8):1054–61.

68. Baldwin DS, Aitchison K, Bateson A, Curran HV, Davies S, Leonard B, et al. Benzodiazepines: Risks and benefits. A reconsideration. J Psychopharmacol. 2013 Nov;27(11):967–71.

69. Michelini S, Cassano GB, Frare F, Perugi G. Long-term use of benzodiazepines: tolerance, dependence and clinical problems in anxiety and mood disorders. Pharmacopsychiatry. 1996 Jul;29(4):127-34.

70. Longo LP, Johnson B. Addiction: Part I. Benzodiazepines--side effects, abuse risk and alternatives. American Family Physician. 2000 Apr 1;61(7):2121-8.

71. Bateson A. Basic Pharmacologic Mechanisms Involved in Benzodiazepine Tolerance and Withdrawal. CPD. 2002 Jan 1;8(1):5–21.

72. Smedslund G, Berg RC, Hammerstrøm KT, Steiro A, Leiknes KA, Dahl HM, et al. Motivational interviewing for substance abuse. Campbell Systematic Reviews. 2011 Jan;7(1):1–126.

73. Petitjean S, Ladewig D, Meier CR, Amrein R, Wiesbeck GA. Benzodiazepine prescribing to the Swiss adult population: results from a national survey of community pharmacies: International Clinical Psychopharmacology. 2007 Sep;22(5):292–8.

74. Neutel CI. The epidemiology of long-term benzodiazepine use. Int Rev Psychiatry. 2005 Jan 1;17(3):189–97.

75. Huang B, Dawson DA, Stinson FS, Hasin DS, Ruan WJ, Saha TD, Smith SM, Goldstein RB, Grant BF. Prevalence, correlates, and comorbidity of nonmedical prescription drug use and drug use disorders in the United States: Results of the National Epidemiologic Survey on Alcohol and Related Conditions. J Clin Psychiatry. 2006 Jul;67(7):1062-73.

76. Moylan S, Giorlando F, Nordfjærn T, Berk M. The role of alprazolam for the treatment of panic disorder in Australia. Aust N Z J Psychiatry. 2012 Mar 1;46(3):212–24.

77. Ait-Daoud N, Hamby AS, Sharma S, Blevins D. A Review of Alprazolam Use, Misuse, and Withdrawal. Journal of Addiction Medicine. 2018 Jan;12(1):4–10.

78. Buffett-Jerrott SE, Stewart SH. Cognitiveand sedative effects of benzodiazepine use. Curr Pharm Des. 2002;8:45-58.

79. Tanaka E. Clinically significant pharmacokinetic drug interactions with benzodiazepines. J Clin Pharm Ther. 1999 Oct;24(5):347–55.

80. Ashton H. Guidelines for the Rational Use of Benzodiazepines. Drugs. 1994 Jul 1;48(1):25–40.

81. Lader M. Clinical pharmacology of benzodiazepines. Annu Rev Med. 1987;38:19-28.

82. Agencia Española de Medicamentos y Productos Sanitarios (AEMPS). Ficha técnica Valium® 10 mg comprimidos. [Internet] Available from: https://cima.aemps.es/cima/pdfs/es/ft/39409/39409_ft.pdf

83. Garcés-Vieira MV, Suárez-Escudero JC. Neuroplasticidad: aspectos bioquímicos y neurofisiológicos. 2014;(1):14.

84. Back DJ, Orme ML. Pharmacokinetic drug interactions with oral contraceptives. Clin Pharmacokinet. 1990 Jun;18(6):472-84.

85. Agencia Española de Medicamentos y Productos Sanitarios (AEMPS). Ficha técnica Theo-Dur® 100 mg comprimidos de liberación prolongada. [Internet] Available from: https://cima.aemps.es/cima/pdfs/es/ft/56199/FichaTecnica_56199.html.pdf

86. Observatorio de Resultados. Informe 2018. Murcia: Subdirección General de Calidad Asistencial, Seguridad y Evaluación. Dirección General de Asistencia Sanitaria. Servicio Murciano de Salud; 2021.

87. Agencia Española de Medicamentos y Productos Sanitarios (AEMPS). Utilización de medicamentos ansiolíticos e hipnóticos en España. [Internet] Available from: https://www.aemps.gob.es/medicamentos-de-uso-humano/observatorio-de-uso-de-medicamentos/informes-ansioliticos-hipnoticos/

88. Díaz-Gutiérrez MJ, Martínez-Cengotitabengoa M, Bermúdez-Ampudia C, García S, López P, Martínez-Cengotitabengoa M, et al. Overdosing of benzodiazepines/Z-drugs and falls in older adults: Costs for the health system. Experimental Gerontology. 2018 Sep;110:42–5.

89. Panneman MJM, Goettsch WG, Kramarz P, Herings RMC. The Costs of Benzodiazepine-Associated Hospital-Treated Fall Injuries in the EU: A Pharmo Study: Drugs & Aging. 2003;20(11):833–9.

90. Gorevski E, Bian B, Kelton CM, Martin Boone JE, Guo JJ. Utilization, Spending, and Price Trends for Benzodiazepines in the US Medicaid Program: 1991-2009. Ann Pharmacother. 2012 Apr 1;46(4):503–12.

91. Substance Abuse and Mental Health Services Administration. Center for Behavioral Health Statistics and Quality: Drug Abuse Warning Network, 2008: National Estimates of Drug-Related Emergency Department Visits. Rockville, MD: Substance Abuse and Mental Health Services Administration; 2011.

92. Morgan S, University of British Columbia, Centre for Health Services and Policy Research. The Canadian Rx atlas. Vancouver: Centre for Health Services and Policy Research, University of British Columbia; 2008. [Internet] Available from: http://www.deslibris.ca/ID/216073

93. Dionne P-A, Vasiliadis H-M, Latimer E, Berbiche D, Preville M. Economic Impact of Inappropriate Benzodiazepine Prescribing and Related Drug Interactions Among Elderly Persons. PS. 2013 Apr;64(4):331–8.

94. Alonso J, Petukhova M, Vilagut G, Chatterji S, Heeringa S, Üstün TB, et al. Days out of role due to common physical and mental conditions: results from the WHO World Mental Health surveys. Mol Psychiatry. 2011 Dec;16(12):1234–46.

95. Grande I, Berk M, Birmaher B, Vieta E. Bipolar disorder. The Lancet. 2016 Apr;387(10027):1561–72.

96. Martinez-Aran A, Vieta E, Torrent C, Sanchez-Moreno J, Goikolea J, Salamero M, et al. Functional outcome in bipolar disorder: the role of clinical and cognitive factors. Bipolar Disorders. 2007 Feb;9(1–2):103–13.

97. Grande I, Goikolea JM, de Dios C, González-Pinto A, Montes JM, Saiz-Ruiz J, et al. Occupational disability in bipolar disorder: analysis of predictors of being on severe disablement benefit (PREBIS study data): Occupational disability in BD. Acta Psychiatr Scand. 2013 May;127(5):403–11.

98. Gardner HH, Kleinman NL, Brook RA, Rajagopalan K, Brizee TJ, Smeeding JE. The economic impact of bipolar disorder in an employed population from an employer perspective. J Clin Psychiatry. 2006 Aug;67:1209–18.

99. Fiedorowicz JG, Palagummi NM, Forman-Hoffman VL, Miller DD, Haynes WG. Elevated Prevalence of Obesity, Metabolic Syndrome, and Cardiovascular Risk Factors in Bipolar Disorder. Annals of Clinical Psychiatry. 2008 Aug;20(3):131–7.

100. Kilbourne AM, Cornelius JR, Han X, Pincus HA, et al. Burden of general medical conditions among individuals with bipolar disorder. Bipolar Disorders. 2004 Oct;6:368-73.

101. Schaffer A, Isometsä ET, Tondo L, H Moreno D, Turecki G, Reis C, et al. International Society for Bipolar Disorders Task Force on Suicide: meta-analyses and meta-regression of correlates of suicide attempts and suicide deaths in bipolar disorder. Bipolar Disord. 2015 Feb;17(1):1–16.

102. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5). Arlington, VA: American Psychiatric Assoc Publishing; 2013.

103. Wittchen H-U, Jacobi F. Size and burden of mental disorders in Europe—a critical review and appraisal of 27 studies. European Neuropsychopharmacology. 2005 Aug;15(4):357–76.

104. Gale C, Davidson O. Generalised anxiety disorder. BMJ. 2007 Mar 17;334(7593):579–81.

105. Kanwar A, Malik S, Prokop LJ, Sim LA, Feldstein D, Wang Z, Murad MH. The association between anxiety disorders and suicidal behaviors: a systematic review and meta-analysis. Depress Anxiety. 2013 Oct;30(10):917-29.

106. Butnoriene J, Bunevicius A, Saudargiene A, Nemeroff CB, Norkus A, Ciceniene V, et al. Metabolic syndrome, major depression, generalized anxiety disorder, and ten-year all-cause and cardiovascular mortality in middle aged and elderly patients. International Journal of Cardiology. 2015 Jul;190:360–6.

107. Martens EJ, de Jonge P, Na B, Cohen BE, Lett H, Whooley MA. Scared to Death? Generalized Anxiety Disorder and Cardiovascular Events in Patients With Stable Coronary Heart Disease: The Heart and Soul Study. Arch Gen Psychiatry. 2010 Jul 1;67(7):750-8.

108. DeMartini J, Patel G, Fancher TL. Generalized Anxiety Disorder. Ann Intern Med. 2019 Apr 2;170(7):ITC49-64.

109. Ipser JC, Carey P, Dhansay Y, Fakier N, Seedat S, Stein DJ. Pharmacotherapy augmentation strategies in treatment-resistant anxiety disorders. Cochrane Common Mental Disorders Group, editor. Cochrane Database of Systematic Reviews. 2006 Oct 18;(4)CD005473.

110. Brawman-Mintzer O, Knapp RG, Nietert PJ. Adjunctive risperidone in generalized anxiety disorder: a double-blind, placebo-controlled study. J Clin Psychiatry. 2005 Oct;66(10):1321-5.

111. Baldwin DS, Anderson IM, Nutt DJ, Bandelow B, Bond A, Davidson JRT, et al. Evidence-based guidelines for the pharmacological treatment of anxiety disorders: recommendations from the British Association for Psychopharmacology. J Psychopharmacol. 2005 Nov;19(6):567–96.

112. Gorman JM. Treating Generalized Anxiety Disorder. J Clin Psychiatry. 2003;64Suppl2:24-9.

113. World Health Organization (WHO). "Investing In Mental Health." 2003. [Internet] Available from: http://www.who.int/mental_health/media/investing_mnh.pdf.

114. Battle DE. Diagnostic and Statistical Manual of Mental Disorders (DSM). Codas. 2013;25(2):191-2

115. Zhao D, Wu Z, Zhang H, Mellor D, Ding L, Wu H, et al. Somatic symptoms vary in major depressive disorder in China. Comprehensive Psychiatry. 2018 Nov;87:32–7.

116. Murphy JA, Byrne GJ. Prevalence and correlates of the proposed DSM-5 diagnosis of Chronic Depressive Disorder. Journal of Affective Disorders. 2012 Jul;139(2):172–80.

117. Angst J, Gamma A, Rössler W, Ajdacic V, Klein DN. Long-term depression versus episodic major depression: Results from the prospective Zurich study of a community sample. Journal of Affective Disorders. 2009 May;115(1–2):112–21.

118. Dean J, Keshavan M. The neurobiology of depression: An integrated view. Asian Journal of Psychiatry. 2017 Jun;27:101–11.

119. Fava M, Rush AJ, Alpert JE, Balasubramani GK, Wisniewski SR, Carmin CN, et al. Difference in Treatment Outcome in Outpatients With Anxious Versus Nonanxious Depression: A STAR*D Report. AJP. 2008 Mar;165(3):342–51.

120. Davidson JR. Major depressive disorder treatment guidelines in America and Europe. J Clin Psychiatry. 2010;71SupplE1:e04.

121. Bauer M, Adli M, Ricken R, Severus E, Pilhatsch M. Role of lithium augmentation in the management of major depressive disorder. CNS Drugs. 2014 Apr;28(4):331-42.

122. Lieberman JA, First MB. Psychotic Disorders. Ropper AH, editor. N Engl J Med. 2018 Jul 19;379(3):270–80.

123. Arciniegas DB. Psychosis. Continuum (Minneap Minn). 2015 Jun;21(3 Behavioral Neurology and Neuropsychiatry):715-36.

124. Castagnini A, Berrios GE. Acute and transient psychotic disorders (ICD-10 F23): a review from a European perspective. Eur Arch Psychiatry Clin Neurosci. 2009 Dec;259(8):433–43.

125. Singh SAP, Burns T, Amin S, Jones PB, Harrison G. Acute and transient psychotic disorders: precursors, epidemiology, course and outcome. Br J Psychiatry. 2004 Dec;185:452-9.

126. Englisch S, Zink M. Akute psychotische Störungsbilder. Fortschr Neurol Psychiatr. 2020 Feb:88(2):121-38.

127. Jablensky A. The 100-year epidemiology of schizophrenia. Schizophrenia Research. 1997 Dec;28:111-25.

128. Murray RM, Van Os J. Predictors of outcome in schizophrenia. Journal of Clinical Psychopharmacology. 1998 Apr;18(suppl 1):2S–4S.

129. Harrison PJ, Owen MJ. Genes for schizophrenia? Recent findings and their pathophysiological implications. The Lancet. 2003 Feb;361(9355):417–9.

130. Thaker GK, Carpenter WT. Advances in schizophrenia. Nat Med. 2001 Jun;7(6):667–71.

131. Immonen J, Jääskeläinen E, Korpela H, Miettunen J. Age at onset and the outcomes of schizophrenia: A systematic review and meta-analysis: Age at onset and the outcomes of schizophrenia. Early Intervention in Psychiatry. 2017 Dec;11(6):453–60.

132. Mueser KT, McGurk SR. Schizophrenia (Seminar). The Lancet. 2004 Jun; 363(9426):2063–72.

133. Regier DA. Comorbidity of mental disorders with alcohol and other drug abuse. Results from the Epidemiologic Catchment Area (ECA) Study. JAMA: The Journal of the American Medical Association. 1990 Nov 21;264(19):2511–8.

134. de Leon J, Dadvand M, Canuso C, White AO, Stanilla JK, Simpson GM. Schizophrenia and smoking: an epidemiological survey at a state hospital. Am J Psychiatry. 1995;152:453–55.

135. Rosenberg SD, Goodman LA, Osher FC, Swartz MS, Essock SM, Butterfield MI, et al. Prevalence of HIV, hepatitis B, and hepatitis C in people with severe mental illness. Am J Public Health. 2001 Jan;91(1):31–7.

136. Brown S. Excess mortality of schizophrenia: A meta-analysis. Br J Psychiatry. 1997 Dec;171(6):502–8.

137. Mueser KT, Rosenberg SD, Goodman LA, Trumbetta SL. Trauma, PTSD, and the course of severe mental illness: an interactive model. Schizophrenia Research. 2002 Jan;53(1–2):123–43.

138. Susser E, Struenin EL, Conover S. Psychiatric problems in homeless men: Lifetime psychosis, substance use, and current distress in new arrivals at New York City shelters. Arch Cen Psychiatry. 1989;46:845-50.

139. Huppert JD, Smith TE. Longitudinal Analysis of Subjective Quality of Life in Schizophrenia: Anxiety as the Best Symptom Predictor: The Journal of Nervous and Mental Disease. 2001 Oct;189(10):669–75.

140. Addington D, Addington J, Patten S. Depression in people with firstepisode schizophrenia. Br J Psychiatry. 1998;172(suppl 33):90–92.

141. Bartels SJ, Drake RE, Wallach MA, Freeman DH. Characteristic hostility in schizophrenic outpatients. Schizophr Bull. 1991;17:163–71.

142. Inskip H, Harris C, Barraclough B. Lifetime risk of suicide for affective disorder, alcoholism and schizophrenia. Br J Psychiatry. 1998 Jan;172(1):35–7.

143. Malhi GS, Green M, Fagiolini A, Peselow ED, Kumari V. Schizoaffective disorder: diagnostic issues and future recommendations. Bipolar Disorders. 2008 Feb;10(1p2):215–30.

144. Alphs L, Fu D-J, Turkoz I. Paliperidone for the treatment of schizoaffective disorder. Expert Opinion on Pharmacotherapy. 2016 Apr 12;17(6):871–83.

145. Nasrallah H, Goldberg J, Correll C. Differential diagnosis and therapeutic management of schizoaffective disorder. Annals of clinical psychiatry : official journal of the American Academy of Clinical Psychiatrists. 2010 Nov 1;22:S1-12.

146. Cheniaux E, Landeira-Fernandez J, Lessa Telles L, Lessa JLM, Dias A, Duncan T, et al. Does schizoaffective disorder really exist? A systematic review of the studies that compared schizoaffective disorder with schizophrenia or mood disorders. Journal of Affective Disorders. 2008 Mar;106(3):209–17.

147. Vardaxi CCh, Gonda X, Fountoulakis KN. Life events in schizoaffective disorder: A systematic review. Journal of Affective Disorders. 2018 Feb;227:563–70.

148. Olfson M, Marcus SC, Wan GJ. Treatment Patterns for Schizoaffective Disorder and Schizophrenia Among Medicaid Patients. 2009;60(2):7.

149. Cosoff SJ, Hafner RJ. The Prevalence of Comorbid Anxiety in Schizophrenia, Schizoaffective Disorder and Bipolar Disorder. Aust N Z J Psychiatry. 1998 Feb 1;32(1):67–72.

150. Bartoli F, Crocamo C, Caslini M, Clerici M, Carrà G. Schizoaffective disorder and metabolic syndrome: A meta-analytic comparison with schizophrenia and other non-affective psychoses. Journal of Psychiatric Research. 2015 May 11;66–67:127–34.

151. González-Rodríguez A, Esteve M, Álvarez A, Guárdia A, Monreal JA, Palao D, Labad J. What We Know and Still Need to Know about Gender Aspects of Delusional Disorder: A Narrative Review of Recent Work. J Psychiatry Brain Sci. 2019; [Internet] Available from: https://jpbs.hapres.com/htmls/JPBS_1023_Detail.html

152. Grover S, Biswas P, Avasthi A. Delusional disorder: Study from North India. Psychiatry Clin Neurosci. 2007 Oct;61(5):462–70.

153. Peralta V, Cuesta MJ. An empirical study of five sets of diagnostic criteria for delusional disorder. Schizophrenia Research. 2019 Jul;209:164–70.

154. Skelton M, Khokhar WA, Thacker SP. Treatments for delusional disorder. Cochrane Schizophrenia Group, editor. Cochrane Database of Systematic Reviews. 2015 May 22.

155. Huang Y, Kotov R, de Girolamo G, Preti A, Angermeyer M, Benjet C, et al. DSM–IV personality disorders in the WHO World Mental Health Surveys. Br J Psychiatry. 2009 Jul;195(1):46–53.

156. Lenzenweger MF, Lane MC, Loranger AW, Kessler RC. DSM-IV Personality Disorders in the National Comorbidity Survey Replication. Biological Psychiatry. 2007 Sep;62(6):553–64.

157. Grant B, Hasin D, Stinson F, Dawson D, Chou S, Ruan W, et al. Prevalence, Correlates, and Disability of Personality Disorders in the United States: Results From the National Epidemiologic Survey on Alcohol and Related Conditions. The Journal of clinical psychiatry. 2004 Aug 1;65:948–58.

158. Ekselius L. Personality disorder: a disease in disguise. Upsala Journal of Medical Sciences. 2018 Oct 2;123(4):194–204.

159. Markovitz PJ. Recent Trends in the Pharmacotherapy of Personality Disorders. Journal of Personality Disorders. 2004 Feb;18(1):90–101.

160. Tandon R. Antipsychotics in the Treatment of Schizophrenia: An Overview. J Clin Psychiatry. 2011 Dec;72(suppl 1). [Internet] Available from: http://article.psychiatrist.com/?ContentType=START&ID=10007704

161. Krogmann A, Peters L, von Hardenberg L, Bödeker K, Nöhles VB, Correll CU. Keeping up with the therapeutic advances in schizophrenia: a review of novel and emerging pharmacological entities. CNS Spectr. 2019 Aug;24(S1):38–69.

162. Divac N, Prostran M, Jakovcevski I, Cerovac N. Second-Generation Antipsychotics and Extrapyramidal Adverse Effects. BioMed Research International. 2014;2014:1–6.

163. Slim M, Medina-Caliz I, Gonzalez-Jimenez A, Cabello MR, Mayoral-Cleries F, Lucena MI, et al. Hepatic Safety of Atypical Antipsychotics: Current Evidence and Future Directions. Drug Saf. 2016 Oct;39(10):925–43.

164. Shapiro DA, Renock S, Arrington E, Chiodo LA, Liu L-X, Sibley DR, et al. Aripiprazole, A Novel Atypical Antipsychotic Drug with a Unique and Robust Pharmacology. Neuropsychopharmacol. 2003 Aug;28(8):1400–11.

165. Meltzer HY. An atypical compound by any other name is still a. Psychopharmacology. 2000 Jan 21;148(1):16–9.

166. Vasilyeva I, Biscontri RG, Enns MW, Metge CJ, Alessi-Severini S. Movement Disorders in Elderly Users of Risperidone and First Generation Antipsychotic Agents: A Canadian Population-Based Study. PLOS ONE. 2013;8(5):7.

167. Meltzer HY. Update on Typical and Atypical Antipsychotic Drugs. Annu Rev Med. 2013 Jan 14;64(1):393–406.

168. Ward KM, Citrome L. Antipsychotic-Related Movement Disorders: Drug-Induced Parkinsonism vs. Tardive Dyskinesia—Key Differences in Pathophysiology and Clinical Management. Neurol Ther. 2018 Dec;7(2):233–48.

169. Arya D, Khan T, Margolius AJ, Fernandez HH. Tardive Dyskinesia: Treatment Update. Curr Neurol Neurosci Rep. 2019 Sep;19(9):69.

170. Arvanitis LA, Miller BG. Multiple fixed doses of "Seroquel" (quetiapine) in patients with acute exacerbation of schizophrenia: A comparison with haloperidol and placebo. Biological Psychiatry. 1997 Aug;42(4):233-46.

171. Beasley CM Jr, Tollefson G, Tran P, Satterlee W, Sanger T, Hamilton S. Olanzapine versus placebo and haloperidol: acute phase results of the North American double-blind olanzapine trial. Neuropsychopharmacology. 1996 Feb;14(2):111-23.

172. Lieberman JA. Managing Anticholinergic Side Effects. Prim Care Companion J Clin Psychiatry. :4.

173. Kaar SJ, Natesan S, McCutcheon R, Howes OD. Antipsychotics: Mechanisms underlying clinical response and side-effects and novel treatment approaches based on pathophysiology. Neuropharmacology. 2020 Aug;172:107704.

174. MacKenzie NE, Kowalchuk C, Agarwal SM, Costa-Dookhan KA, Caravaggio F, Gerretsen P, et al. Antipsychotics, Metabolic Adverse Effects, and Cognitive Function in Schizophrenia. Front Psychiatry. 2018 Dec;9:622.

175. Rummel-Kluge C, Komossa K, Schwarz S, Hunger H, Schmid F, Lobos CA, et al. Head-to-head comparisons of metabolic side effects of second generation antipsychotics in the treatment of schizophrenia: A systematic review and meta-analysis. Schizophrenia Research. Nov;123(2-3):225-33.

176. Thomas SP, Nandhra HS, Singh SP. Pharmacologic treatment of first-episode schizophrenia: a review of the literature. Prim Care Companion CNS Disord. 2012;14(1):PCC.11r01198.

177. Allison DB, Chandler LP, Infante MC. Antipsychotic-Induced Weight Gain: A Comprehensive Research Synthesis. Am J Psychiatry. 1999;11.

178. Howes OD, Smith S, Gaughran FP, Amiel SA, Murray RM, Pilowsky LS. The Relationship Between Prolactin Levels and Glucose Homeostasis in Antipsychotic-treated Schizophrenic Patients. Journal of Clinical Psychopharmacology. 2006 Dec;26(6):629-31.

179. Johnsen E, Kroken RA, Abaza M, Olberg H, Jørgensen HA. Antipsychotic-induced hyperprolactinemia: a cross-sectional survey. J Clin Psychopharmacol. 2008 Dec;28(6):686-90.

180. Lally J, Ajnakina O, Stubbs B, Williams HR, Colizzi M, Carra E, et al. Hyperprolactinaemia in first episode psychosis - A longitudinal assessment. Schizophrenia Research. 2017 Nov;189:117-25.

181. Waldinger MD. Psychiatric disorders and sexual dysfunction. Handbook of Clinical Neurology [Internet]. Elsevier; 2015 [Internet]. p. 469-89. Available from: https://linkinghub.elsevier.com/retrieve/pii/B9780444632470000274

182. Selim K, Kaplowitz N. Hepatotoxicity of psychotropic drugs. Hepatology. 1999 May;29(5):1347-51.

183. Haverkamp W, Mönnig G, Schulze-Bahr E, Haverkamp F, Breithardt G. Physician-induced torsade de pointes—therapeutic implications. Cardiovasc Drugs Ther. 2002 Mar;16(2):101-9.

184. Crouch MA, Limon L, Cassano AT. Clinical Relevance and Management of Drug-Related QT Interval Prolongation. Pharmacotherapy. 2003 Jul;23(7):881-908.

185. Wiciński M, Węclewicz MM. Clozapine-induced agranulocytosis/granulocytopenia: mechanisms and monitoring. Current Opinion in Hematology. 2018 Jan;25(1):22-8.

186. Hall R, Smith A, Edwards JG. Haematological safety of antipsychotic drugs. Expert Opin Drug Saf. 2003;5.

187. Atkin K, Kendall F, Gould D, Freeman H, Lieberman J, O'Sullivan D. Neutropenia and Agranulocytosis in Patients Receiving Clozapine in the UK and Ireland. Br J Psychiatry. 1996 Oct;169(4):483-8.

188. Spanarello S, La Ferla T. The pharmacokinetics of long-acting antipsychotic medications. Curr Clin Pharmacol. 2014;9(3):310-7.

189. Remenar JF. Making the Leap from Daily Oral Dosing to Long-Acting Injectables: Lessons from the Antipsychotics. Mol Pharmaceutics. 2014 Jun;11(6):1739-49.

190. Agencia Española de Medicamentos y Productos Sanitarios (AEMPS). Ficha técnica Risperdal Consta® 25 mg polvo y disolvente para suspensión de liberación prolongada para inyección. [Internet] Available from: https://cima.aemps.es/cima/pdfs/ft/65214/FT_65214.pdf

191. Knox ED, Stimmel GL. Clinical review of a long-acting, injectable formulation of risperidone. Clinical Therapeutics. Dec;26(12):1994-2002.

192. Mauri MC, Paletta S, Di Pace C, Reggiori A, Cirnigliaro G, Valli I, et al. Clinical Pharmacokinetics of Atypical Antipsychotics: An Update. Clin Pharmacokinet. 2018 Dec;57(12):1493-528.

193. Eli Lilly and Company, 2009. Ficha técnica Zyprexa® Relprevv®. [Internet] Available from: https://uspl.lilly.com/zyprexa-relprevv/zyprexarelprevv.html#pi

194. Janssen Pharmaceuticals, Inc. 2009. Ficha técnica Invega® Sustenna®. (paliperidone palmitate) package insert. [Internet] Available from: https://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/INVEGA+SUSTENNA-pi.pdf

195. Jann MW, Penzak SR. Long-Acting Injectable Second-Generation Antipsychotics: An Update and Comparison Between Agents. CNS Drugs. 2018 Mar;32(3):241–57.

196. Salzman P, Raoufinia A, Legacy S, Such P, Eramo A. Plasma concentrations and dosing of 2 long-acting injectable formulations of aripiprazole. NDT. 2017 Apr;Volume 13:1125-9.

197. Citrome L. Aripiprazole long-acting injectable formulations for schizophrenia: aripiprazole monohydrate and aripiprazole lauroxil. Expert Review of Clinical Pharmacology. 2016 Feb;9(2):169-86.

198. Agencia Española de Medicamentos y Productos Sanitarios (AEMPS). Ficha técnica Abilify® Maintena® 300 mg polvo y disolvente para suspensión

de liberación prolongada inyectable. [Internet] Available from: https://cima.aemps.es/cima/dochtml/ft/113882001/FT_113882001.html

199. Alkermes, Inc. 2015. Ficha técnica Aristada™. [Internet] Available from: https://www.aristada.com/downloadables/ARISTADA-PI.pdf

200. Clark I, Taylor D. Newer Formulations of Risperidone: Role in the Management of Psychotic Disorders. CNS Drugs. 2020 Aug;34(8):841-52.

201. Peitl V, Vlahović D. Paliperidone Palmitate 6-month (PP6M). Arch Psychiatry Res. 2021 Jun 1;57(2):229–32.

202. Bossini L, Casolaro I, Koukouna D, Cecchini F, Fagiolini A. Off-label uses of trazodone: a review. Expert Opinion on Pharmacotherapy. 2012 Aug;13(12):1707-17.

203. Khouzam HR. A review of trazodone use in psychiatric and medical conditions. Postgraduate Medicine. 2017 Jan;129(1):140-8.

204. Peña E, Mata M, López-Manzanares L, Kurtis M, Eimil M, Martínez-Castrillo JC, et al. Antidepresivos en la enfermedad de Parkinson. Recomendaciones del grupo de trastornos del movimiento de la Asociación Madrileña de Neurología. Neurología. 2018 Jul;33(6):395-402.

205. Bull SA, Hunkeler EM, Lee JY, Rowland CR, Williamson TE, Schwab JR, et al. Discontinuing or Switching Selective Serotonin-Reuptake Inhibitors. :7.

206. Carvalho AF, Sharma MS, Brunoni AR, Vieta E, Fava GA. The Safety, Tolerability and Risks Associated with the Use of Newer Generation Antidepressant Drugs: A Critical Review of the Literature. Psychother Psychosom. 2016;85(5):270-88.

207. Schwasinger-Schmidt TE, Macaluso M. Other Antidepressants. Handb Exp Pharmacol. 2019;250:325-355.

208. Stahl SM, Grady MM, Moret C, Briley M. SNRIs: The Pharmacology, Clinical Efficacy, and Tolerability in Comparison with Other Classes of Antidepressants. CNS Spectrums. 2005;10(9):16.

209. Khalid MM, Waseem M. Tricyclic Antidepressant Toxicity. 2021 Feb 10. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan–.

[Internet] Available from: https://www.ncbi.nlm.nih.gov/books/NBK430931/#_NBK430931_pubdet_

210. Samalin L, Murru A, Vieta E. Management of inter-episodic periods in patients with bipolar disorder. Expert Rev Neurother. 2016 Jun;16(6):659-70.

211. Grunze H. Lithium in the acute treatment of bipolar disorders?a stocktaking. European Archives of Psychiatry and Clinical Neuroscience. 2003 Jun;253(3):115-9.

212. Shim I, Woo Y, Kim M-D, Bahk W-M. Antidepressants and Mood Stabilizers: Novel Research Avenues and Clinical Insights for Bipolar Depression. IJMS. 2017 Nov 13;18(11):2406.

213. Fountoulakis KN, Grunze H, Panagiotidis P, Kaprinis G. Treatment of bipolar depression: An update. Journal of Affective Disorders. 2008 Jul;109(1–2):21–34.

214. Gyulai L, Bowden CL, McElroy SL, Calabrese JR, Petty F, Swann AC, et al. Maintenance Efficacy of Divalproex in the Prevention of Bipolar Depression. Neuropsychopharmacol. 2003 Jul;28(7):1374-82.

215. Grande I, Berk M, Birmaher B, Vieta E. Bipolar disorder. The Lancet. 2016 Apr;387(10027):1561-72.

216. Woo YS, Lee JG, Jeong J-H, Kim M-D, Sohn I, Shim S-H, et al. Korean Medication Algorithm Project for Bipolar Disorder: third revision. Neuropsychiatric Disease and Treatment. 2014;14.

217. Grunze H, Vieta E, Goodwin GM, Bowden C, Licht RW, Möller H-J, et al. The World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for the Biological Treatment of Bipolar Disorders: Update 2012 on the long-term treatment of bipolar disorder. :66.

218. Yatham LN, Kennedy SH, Parikh SV, Schaffer A, Beaulieu S, Alda M, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) collaborative update of CANMAT guidelines for the management of patients with bipolar disorder: update 2013: CANMAT guidelines for bipolar disorder. Bipolar Disorders. 2013 Feb;15(1):1-44.

219. Goodwin G, Consensus Group of the British Association for Psychopharmacology. Evidence-based guidelines for treating bipolar disorder:

revised second edition—recommendations from the British Association for Psychopharmacology. J Psychopharmacol. 2009 Jun;23(4):346–88.

220. National Collaborating Centre for Mental Health (UK). Bipolar Disorder: The NICE Guideline on the Assessment and Management of Bipolar Disorder in Adults, Children and Young People in Primary and Secondary Care. London: The British Psychological Society and The Royal College of Psychiatrists; 2014 Sep.

221. Goodwin G, Haddad P, Ferrier I, Aronson J, Barnes T, Cipriani A, et al. Evidence-based guidelines for treating bipolar disorder: Revised third edition recommendations from the British Association for Psychopharmacology. J Psychopharmacol. 2016 Jun;30(6):495-553.

222. Nath M, Gupta V. Mood Stabilizers. 2021 Feb 6. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2021 Jan–. [Internet] Available from: https://www.ncbi.nlm.nih.gov/books/NBK556141/

223. Miziak B, Błaszczyk B, Chrościńska-Krawczyk M, Danilkiewicz G, Jagiełło-Wójtowicz E, Czuczwar SJ. The problem of osteoporosis in epileptic patients taking antiepileptic drugs. Expert Opinion on Drug Safety. 2014 Jul;13(7):935-46.

224. Goh KK, Chen C-H, Lu M-L. Topiramate mitigates weight gain in antipsychotic-treated patients with schizophrenia: meta-analysis of randomised controlled trials. International Journal of Psychiatry in Clinical Practice. 2019 Jan;23(1):14-32.

225. Bachhuber MA, Hennessy S, Cunningham CO, Starrels JL. Increasing Benzodiazepine Prescriptions and Overdose Mortality in the United States, 1996–2013. Am J Public Health. 2016 Apr;106(4):686–8.

226. Maust DT, Lin LA, Blow FC. Benzodiazepine Use and Misuse Among Adults in the United States. PS. 2019 Feb;70(2):97–106.

227. Bénard-Laribière A, Noize P, Pambrun E, Bazin F, Verdoux H, Tournier M, et al. Comorbidities and concurrent medications increasing the risk of adverse drug reactions: prevalence in French benzodiazepine users. Eur J Clin Pharmacol. 2016 Jul;72(7):869–76.

228. van Eijk JThM, Bosma H, Jonkers CCM, Lamers F, Muijrers PEM. Prescribing Antidepressants and Benzodiazepines in the Netherlands: Is

Chronic Physical Illness Involved? Depression Research and Treatment. 2010;2010:1–6.

229. Kapil V, Green JL, Lait CL, Wood DM, Dargan PI. Misuse of benzodiazepines and Z-drugs in the UK. Br J Psychiatry. 2014 Nov;205(5):407–8.

230. Kirby M, Denihan A, Bruce I, Radic A, Coakley D, Lawlor BA. Benzodiazepine use among the elderly in the community. 1999;5.

231. McHugh RK, Geyer RB, Chase AR, Griffin ML, Bogunovic O, Weiss RD. Sex differences in benzodiazepine misuse among adults with substance use disorders. Addictive Behaviors. 2021 Jan;112:106608.

232. Martinez-Cengotitabengoa M, Diaz-Gutierrez MJ, Besga A, Bermúdez-Ampudia C, López P, Rondon MB, et al. Prescripción de benzodiacepinas y caídas en mujeres y hombres ancianos. Revista de Psiquiatría y Salud Mental. 2018 Jan;11(1):12–8.

233. Maclagan LC, Maxwell CJ, Harris DA, Campitelli MA, Diong C, Lapane KL, et al. Sex Differences in Antipsychotic and Benzodiazepine Prescribing Patterns: A Cohort Study of Newly Admitted Nursing Home Residents with Dementia in Ontario, Canada. Drugs Aging. 2020 Nov;37(11):817–27.

234. Agarwal SD, Landon BE. Patterns in Outpatient Benzodiazepine Prescribing in the United States. JAMA Netw Open. 2019 Jan 25;2(1):e187399.

235. Campanha AM, Ravagnani B, Milhorança IA, Bernik MA, Viana MC, Wang Y-P, et al. Benzodiazepine use in Sao Paulo, Brazil. Clinics. 2020;75:e1610.

236. Hunt GE, Large MM, Cleary M, Lai HMX, Saunders JB. Prevalence of comorbid substance use in schizophrenia spectrum disorders in community and clinical settings, 1990–2017: Systematic review and meta-analysis. Drug and Alcohol Dependence. 2018 Oct;191:234–58.

237. Crawford MJ, Kakad S, Rendel C, Mansour NA, Crugel M, Liu KW, et al. Medication prescribed to people with personality disorder: the influence of

patient factors and treatment setting: Medication prescribed to people with personality disorder. Acta Psychiatrica Scandinavica. 2011 Nov;124(5):396–402.

238. Martín-Blanco A, Ancochea A, Soler J, Elices M, Carmona C, Pascual JC. Changes over the last 15 years in the psychopharmacological management of persons with borderline personality disorder. Acta Psychiatr Scand. 2017 Sep;136(3):323–31.

239. Toftdahl NG, Nordentoft M, Hjorthøj C. Prevalence of substance use disorders in psychiatric patients: a nationwide Danish population-based study. Soc Psychiatry Psychiatr Epidemiol. 2016 Jan;51(1):129–40.

240. Votaw VR, Witkiewitz K, Valeri L, Bogunovic O, McHugh RK. Nonmedical prescription sedative/tranquilizer use in alcohol and opioid use disorders. Addictive Behaviors. 2019 Jan;88:48–55.

241. Detke HC, Weiden PJ, Llorca P-M, Choukour M, Watson SB, Brunner E, et al. Comparison of Olanzapine Long-Acting Injection and Oral Olanzapine: A 2-Year, Randomized, Open-Label Study in Outpatients With Schizophrenia. Journal of Clinical Psychopharmacology. 2014 Aug;34(4):426–34.

242. Naloto DCC, Lopes FC, Barberato Filho S, Lopes LC, Del Fiol F de S, Bergamaschi C de C. Prescription of benzodiazepines for adults and older adults from a mental health clinic. Ciênc saúde coletiva. 2016 Apr;21(4):1267–76.

243. Vicente Sánchez MP, Macías Saint-Gerons D, Fuente Honrubia C de la, González Bermejo D, Montero Corominas D, Catalá-López F. Evolución del uso de medicamentos ansiolíticos e hipnóticos en España durante el período 2000-2011. Rev Esp Salud Publica. 2013 Jun;87(3):247–55.

244. Noia AS, Secoli SR, Duarte YA de O, Lebrão ML, Lieber NSR. Fatores associados ao uso de psicotrópicos por idosos residentes no Município de São Paulo. Rev esc enferm USP. 2012 Oct;46(spe):38–43.

245. Pereira L, Freitas O, Netto M. Antidepressivos e Benzodiazepínicos: estudo sobre o uso racional entre usuários do SUS em Ribeirão Preto-SP. Revista de Ciências Farmacêuticas Básica e Aplicada. 2012 Feb 8;33.

246. Alvarenga JM, Firmo JOA, Lima-Costa MF, Uchoa E. Prevalence and sociodemographic characteristics associated with benzodiazepines use among

community dwelling older adults: The Bambuí Health and Aging Study (BHAS). Rev Bras Psiquiatr. 2007;5.

247. Lagnaoui R, Depont F, Fourrier A, Abouelfath A, Bégaud B, Verdoux H, et al. Patterns and correlates of benzodiazepine use in the French general population. Eur J Clin Pharmacol. 2004 Sep;60(7):523–9.

248. Smith AJ, Tett SE. Improving the use of benzodiazepines-Is it possible? A non-systematic review of interventions tried in the last 20 years. BMC Health Serv Res. 2010 Dec;10(1):321.

249. Islam MM, Wollersheim D. A comparison of opioids and benzodiazepines dispensing in Australia. Suppiah V, editor. PLoS ONE. 2019 Aug 19;14(8):e0221438.

250. Murphy Y, Wilson E, Goldner EM, Fischer B. Benzodiazepine Use, Misuse, and Harm at the Population Level in Canada: A Comprehensive Narrative Review of Data and Developments Since 1995. Clin Drug Investig. 2016 Jul;36(7):519–30.

251. Speranza N, Domínguez V, Pagano E, Artagaveytia P, Olmos I, Toledo M, et al. Consumo de benzodiazepinas en la población uruguaya: un posible problema de salud pública:8.

252. Wilhelm S, Schacht A, Wagner T. Use of antipsychotics and benzodiazepines in patients with psychiatric emergencies: Results of an observational trial. BMC Psychiatry. 2008 Dec;8(1):61.

253. Sampson S, Hosalli P, Furtado VA, Davis JM. Risperidone (depot) for schizophrenia. Cochrane Schizophrenia Group, editor. Cochrane Database of Systematic Reviews. 2016 Apr 14; [Internet] Available from: https://doi.wiley.com/10.1002/14651858.CD004161.pub2

254. Baldessarini R, Henk H, Sklar A, Chang J, Leahy L. Psychotropic Medications for Patients With Bipolar Disorder in the United States: Polytherapy and Adherence. Psychiatric Sservices. 2008;59(10):9.

255. Lang K, Korn J, Muser E, Choi JC, Abouzaid S, Menzin J. Predictors of medication nonadherence and hospitalization in Medicaid patients with bipolar I disorder given long-acting or oral antipsychotics. Journal of Medical Economics. 2011 Jan;14(2):217–26.

256. Kim H-Y, Lee H-W, Jung S-H, Kang M-H, Bae J-N, Lee J-S, et al. Prescription Patterns for Patients with Schizophrenia in Korea: A Focus on Antipsychotic Polypharmacy. Clin Psychopharmacol Neurosci. 2014 Aug 28;12(2):128–36.

257. Gallego JA, Bonetti J, Zhang J, Kane JM, Correll CU. Prevalence and correlates of antipsychotic polypharmacy: A systematic review and meta-regression of global and regional trends from the 1970s to 2009. Schizophrenia Research. 2012 Jun;138(1):18–28.

258. Victoroff J, Coburn K, Reeve A, Sampson S, Shillcutt S. Pharmacological Management of Persistent Hostility and Aggression in Persons With Schizophrenia Spectrum Disorders: A Systematic Review. J Neuropsychiatry Clin Neurosci. 2014;30.

259. Buoli M, Rovera C, Esposito CM, Grassi S, Cahn W, Altamura AC. The use of long-acting antipsychotics for the management of aggressiveness in schizophrenia: a clinical overview. Clinical Schizophrenia & Related Psychoses. 2018 Jun.

260. Musil R, Obermeier M, Russ P, Hamerle M. Weight gain and antipsychotics: a drug safety review. Expert Opinion on Drug Safety. 2015 Jan 2;14(1):73–96.

261. Huhn M, Nikolakopoulou A, Schneider-Thoma J, Krause M, Samara M, Peter N, et al. Comparative efficacy and tolerability of 32 oral antipsychotics for the acute treatment of adults with multi-episode schizophrenia: a systematic review and network meta-analysis. The Lancet. 2019 Sep;394(10202):939–51.

262. Ribeiro ELA, de Mendonça Lima T, Vieira MEB, Storpirtis S, Aguiar PM. Efficacy and safety of aripiprazole for the treatment of schizophrenia: an overview of systematic reviews. Eur J Clin Pharmacol. 2018 Oct;74(10):1215–33.

263. Salgueiro M, Segarra R. Long-acting injectable second-generation antipsychotics in first-episode psychosis: a narrative review. International Clinical Psychopharmacology. 2019 Mar;34(2):51–6.

264. Wu C-S, Lin Y-J, Liu S-K. Benzodiazepine Use Among Patients With Schizophrenia in Taiwan: A Nationwide Population-Based Survey. 2011;62(8):7.

265. Toto S, Grohmann R, Bleich S, Frieling H, Maier HB, Greil W, et al. Psychopharmacological Treatment of Schizophrenia Over Time in 30 908 Inpatients: Data From the AMSP Study. International Journal of Neuropsychopharmacology. 2019 Sep 1;22(9):560–73.

266. Chakos M, Patel J, Rosenheck R, Glick I, Hammer M, Tapp A, et al. Concomitant Psychotropic Medication Use During Treatment of Schizophrenia Patients: Longitudinal Results from the CATIE Study. Clinical schizophrenia & related psychoses. 2011 Oct 1;5:124–34.

267. McDonnell DP, Landry J, Detke HC. Long-term safety and efficacy of olanzapine long-acting injection in patients with schizophrenia or schizoaffective disorder: a 6-year, multinational, single-arm, open-label study. International Clinical Psychopharmacology. 2014 Nov;29(6):322–31.

268. Dong M, Zeng L-N, Zhang Q, Yang S-Y, Chen L-Y, Najoan E, et al. Prescription of antipsychotic and concomitant medications for adult Asian schizophrenia patients: Findings of the 2016 Research on Asian Psychotropic Prescription Patterns (REAP) survey. Asian Journal of Psychiatry. 2019 Oct;45:74–80.

269. Sim F, Sweetman I, Kapur S, Patel MX. Re-examining the role of benzodiazepines in the treatment of schizophrenia: A systematic review. J Psychopharmacol. 2015 Feb;29(2):212–23.

270. Tiihonen J. Polypharmacy With Antipsychotics, Antidepressants, or Benzodiazepines and Mortality in Schizophrenia. Arch Gen Psychiatry. 2012 May 1;69(5):476.

271. Leucht S, Cipriani A, Spineli L, Mavridis D, Örey D, Richter F, et al. Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. The Lancet. 2013 Sep;382(9896):951–62.

272. Jariyavilas A, Thavichachart N, Kongsakon R, Chantakarn S, Arunpongpaisal S, Chantarasak V, et al. Effects of paliperidone extended release on hostility among Thai patients with schizophrenia. NDT. 2017 Jan;Volume 13:141–6.

273. E. Thomas J, Caballero J, A. Harrington C. The Incidence of Akathisia in the Treatment of Schizophrenia with Aripiprazole, Asenapine and Lurasidone: A Meta-Analysis. CN. 2015 Oct 13;13(5):681–91.

274. Miller CH, Fleischhacker WW. Managing Antipsychotic-Induced Acute and Chronic Akathisia: Drug Safety. 2000;22(1):73–81.

275. Dimitropoulos E, Drogemuller L, Wong K. Evaluation of Concurrent Oral and Long-Acting Injectable Antipsychotic Prescribing at the Minneapolis Veterans Affairs Health Care System. J Clin Psychopharmacol. 2017 Oct;37(5):605–8.

276. Doshi JA, Pettit AR, Stoddard JJ, Zummo J, Marcus SC. Concurrent Oral Antipsychotic Drug Use Among Schizophrenia Patients Initiated on Long-Acting Injectable Antipsychotics Post-Hospital Discharge. Journal of Clinical Psychopharmacology. 2015 Aug;35(4):442–6.

277. Aggarwal N, Sernyak M, Rosenheck R. Prevalence of Concomitant Oral Antipsychotic Drug Use Among Patients Treated With Long-Acting, Intramuscular, Antipsychotic Medications. Journal of clinical psychopharmacology. 2012 Apr 26;32:323–8.

278. Palomares N, Montes A, Díaz-Marsá M, Carrasco JL. Effectiveness of long-acting paliperidone palmitate in borderline personality disorder: International Clinical Psychopharmacology. 2015 Nov;30(6):338–41.

279. Zanarini M, Frankenburg F, Parachini E. A Preliminary, Randomized Trial of Fluoxetine, Olanzapine, and the Olanzapine-Fluoxetine Combination in Women With Borderline Personality Disorder. The Journal of clinical psychiatry. 2004 Aug 1;65:903–7.

280. Paris J. Why Patients With Severe Personality Disorders Are Overmedicated. The Journal of clinical psychiatry. 2015 Apr 1;76:e521.

281. Pascual JC, Martín-Blanco A, Soler J. Twenty-Year Trends in the Psychopharmacological Treatment of Outpatients with Borderline Personality Disorder: A Cross-Sectional Naturalistic Study in Spain. CNS Drugs. 2021 Sep;35(9):1023–32.

282. Gartlehner G, Crotty K, Kennedy S, Edlund MJ, Ali R, Siddiqui M, et al. Pharmacological Treatments for Borderline Personality Disorder: A Systematic

Review and Meta-Analysis. CNS Drugs. 2021 Sep 8; [Internet] Available from: https://link.springer.com/10.1007/s40263-021-00855-4

VII- ANEXOS

VII- ANEXO

ANEXO-1: INFORME COMITÉ DE ÉTICA

UCAM
UNIVERSIDAD CATÓLICA SAN ANTONIO

COMITÉ DE ÉTICA DE LA UCAM

DATOS DEL PROYECTO

Título:	"Patrones de prescripción médica relacionados con el uso de benzodiacepinas en salud mental y en la población general de la Región de Murcia (2016-2017)"	
Investigador Principal	**Nombre**	**Correo-e**
Dr.	Alejandro Galindo Tovar	agalindo@ucam.edu

INFORME DEL COMITÉ

Fecha	**29/03/2019**	**Código**	**CE031914**

Tipo de Experimentación

Investigación experimental clínica con seres humanos	
Utilización de tejidos humanos procedentes de pacientes, tejidos embrionarios o fetales	
Utilización de tejidos humanos, tejidos embrionarios o fetales procedentes de bancos de muestras o tejidos	
Investigación observacional con seres humanos, psicológica o comportamental en humanos	
Uso de datos personales, información genética, etc.	**X**
Experimentación animal	
Utilización de agentes biológicos de riesgo para la salud humana, animal o las plantas	
Uso de organismos modificados genéticamente (OMGs)	

Comentarios Respecto al Tipo de Experimentación
Nada Obsta

Comentarios Respecto a la Metodología de Experimentación
Nada Obsta

UNIVERSIDAD CATÓLICA SAN ANTONIO · COMITÉ DE ÉTICA ·

Universidad Católica San Antonio. Vicerrectorado de Investigación. Salida nº 7340 29/03/2019 19:07:11

UCAM
UNIVERSIDAD CATÓLICA SAN ANTONIO

COMITÉ DE ÉTICA DE LA UCAM

Sugerencias al Investigador

A la vista de la solicitud de informe adjunto por el Investigador y de las recomendaciones anteriormente expuestas el dictamen del Comité es:

Emitir Informe Favorable	**X**
Emitir Informe Desfavorable	
Emitir Informe Favorable condicionado a Subsanación	

MOTIVACIÓN
Incrementará conocimientos en su área

Vº Bº El Presidente,

Fdo.: José Alberto Cánovas Sánchez

El Secretario,

Fdo.: José Alarcón Teruel