2013

REMISIÓN Y FUNCIONALIDAD EN EL TRASTORNO DEPRESIVO MAYOR

TESIS DOCTORAL

Dra. Irene Romera Fernández

Universidad Autónoma de Barcelona. Departamento de Psiquiatría y Medicina Legal.

Directores de Tesis: Dr. Víctor Pérez y Dra. Inmaculada Gilaberte.

Dedicado a Alfredito y a Alfre

"I may say that this is the greatest factor — the way in which the expedition is equipped — the way in which every difficulty is foreseen, and precautions taken for meeting or avoiding it. Victory awaits him who has everything in order — luck, people call it. Defeat is certain for him who has neglected to take the necessary precautions in time; this is called bad luck"

— from The South Pole, by Roald Amundsen

AGRADECIMIENTOS:

A mis padres por enseñarme que el esfuerzo y la preparación son los mejores aliados para obtener logros, por estar siempre ahí y por ser un ejemplo a seguir. A Inmaculada Gilaberte por guiarme en todos estos últimos años, ser una excelente fuente de aprendizaje, por su valor y determinación. A Lilly SA por darme la oportunidad de crecer profesionalmente y llevar a cabo estos proyectos de investigación. A Yuba y a Bubu por su compañía, cariño y apoyo. A todos los pacientes que han participado de forma desinteresada contribuyendo a un mejor conocimiento de la Depresión.

GLOSARIO DE TÉRMINOS:

ACNP: American College of Neuropsychopharmacology

BDI: Beck Depression Inventory

CGI: Clinical Global Impression

CGI-S: Clinical Global Impression-severity

CIE-10: Clasificación internacional de enfermedades- décima versión

DALYs: Disability Adjusted Life Years

DSM-IV: Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition

EEASL: Escala de evaluación de la actividad social y laboral

ESEMeD: European Study of the Epidemiology of Mental Disorders

HAMD17: Escala de Hamilton para la Depression 17 items

IAM: Infarto Agudo de Miocardio

ICD: International Classification of Diseases

MADRS: Montgomery-Asberg Depression Rating Scale

NCS-R= National Comorbidity Survey Replication

NIMH-CDS: National Institute of Mental Health-Collaborative Depression Study

PHQ-7: Patient Health Questionnaire

QIDS-C: Quick Inventory of Depressive Symptomatology- Clinician Rated

QIDS-SR: Quick Inventory of Depressive Symptomatology- Self Report

RDQ: Remission from Depression Questionnaire

SADS: Schedule for Affective Disorders and Schizophrenia

SDS: Sheehan Disability Scale

SOFAS: Social and Occupational Functioning Scale

STAR*D: Sequenced Treatment Alternatives to Relieve Depression

I - INTRODUCCIÓN

TRASTORNO DEPRESIVO MAYOR **Páginas**

ASPECTOS EPIDEMIOLÓGICOS…….....7-9

IMPACTO DE LA ENFERMEDAD……9-11

CRITERIOS DIAGNÓSTICOS……12-14

REMISIÓN EN EL TRASTORNO DEPRESIVO MAYOR

CONCEPTUALIZACIÓN……..15-17

EVALUACIÓN DE LA REMISIÓN: CRITERIOS OPERACIONALES……..17-20

SÍNTOMAS RESIDUALES: DEFINICIÓN Y CARACTERIZACIÓN…….20-22

FACTORES PREDICTIVOS DE SÍNTOMAS RESIDUALES……..22

SÍNTOMAS RESIDUALES Y SU PERSISTENCIA EN EL TIEMPO……22-23

REMISIÓN COMO OBJETIVO TERAPÉUTICO Y SU VALOR PRONÓSTICO……..23-28

REMISIÓN Y FUNCIONALIDAD EN EL TRASTORNO DEPRESIVO MAYOR

FUNCIONALIDAD EN DEPRESIÓN: CONCEPTUALIZACIÓN…….29

MEDICIÓN DE LA FUNCIONALIDAD: INSTRUMENTOS DE EVALUACIÓN...29-32

REMISIÓN SINTOMÁTICA Y RECUPERACIÓN FUNCIONAL COMO OBJETIVO TERAPÉUTICO…….32-33

DETERMINANTES DE LA RECUPERACIÓN FUNCIONAL…….33-37

REMISIÓN Y FUNCIONALIDAD: ASPECTOS SIN RESOLVER…….37-38

II - HIPOTESIS DE TRABAJO Y OBJETIVOS

HIPOTESIS DE TRABAJO Y OBJETIVOS……..……...39-40

OBJETIVOS ESPECÍFICOS Y DISEÑO…….40-42

III - MÉTODO

ESTUDIO I……44-47

ESTUDIO II……47-49

IV - RESULTADOS……51-73

TRABAJO 1: Romera I et al. European Psychiatry 2010

TRABAJO 2: Romera I et al. Psychiatry Research 2011

TRABAJO 3: Romera I et al. BMC Psychiatry 2013

V – DISCUSIÓN……..75-86

VI – CONCLUSIONES……...87-89

VII – BIBLIOGRAFIA…….……91-100

VIII - PUBLICACIONES ADICIONALES……..……..……101-144

1. Romera I, Pérez V. Gilaberte I. Remisión y funcionalidad en el trastorno depresivo mayor. Actas Españolas de Psiquiatria, 2013, en prensa.
2. Romera I et al. Journal of Clinical Psychopharmacology 2012; 32: 479-486
3. Romera I et al. Journal of Affective Disorders 2012;143(1-3):47-55

REMISION Y FUNCIONALIDAD EN EL TRASTORNO DEPRESIVO MAYOR

I -INTRODUCCIÓN

TRASTORNO DEPRESIVO MAYOR: ASPECTOS EPIDEMIOLÓGICOS

El trastorno depresivo mayor se encuentra entre los problemas de salud más comunes, es una de las principales causas de discapacidad y constituye un importante problema de salud pública (Moussavi *et al*., 2007).

A través de varios estudios epidemiológicos realizados en la población general, se ha encontrado una prevalencia- año de la depresión mayor en torno al 4- 7%. Asimismo, la prevalencia-vida encontrada se sitúa alrededor del 11-16% (Alonso *et al.,* 2004; Lepine *et al.,* 1997; Kessler *et al.,* 2003; Gabilondo *et al.,* 2010) [Tabla 1].

Tabla 1: Prevalencia de la depresión en la población general

Región	N	Prevalencia año %(IC 95%)	Prevalencia vida %(IC 95%)	Referencia
Europa* (ESEMeD)	21.425	3,9 (3,6-4,2)	12,8 (12,2-13,4)	Alonso *et al.,* 2004
USA (NCS-R)	9.090	6,6 (5,9-7,3)	16,2 (15,1-17,3)	Kessler *et al.,* 2003
Europa	78.463	6,9†	---	Lepine *et al.,* 1997
España	5473	4,0	10,6	Gabilondo *et al.,* 2010

*Bélgica, Francia, Alemania, Italia, Holanda, España. ESEMeD= European Study of the Epidemiology of Mental Disorders. NCS-R= National Comorbidity Survey Replication. IC=Intervalo de confianza

† Prevalencia en los últimos 6 meses.

Existen diversos factores socio-demográficos que de forma consistente se han visto asociados con una mayor prevalencia de la depresión como, ser mujer, haber estado previamente casado o nunca casado, edades medias, desempleo o incapacidad laboral, menor nivel de educación y bajo nivel económico (Kessler *et al.,* 2003; Alonso

et al., 2004). Cabe reseñar que ser mujer se asocia al doble de riesgo de depresión, incluso algunos estudios han encontrado mayor riesgo, como el proyecto ESEMeD realizado en España que encontró un riesgo de 2,6 (Gabilondo *et al.,* 2010). Dentro de los factores clínicos, se ha visto que la prevalencia aumenta en pacientes con enfermedades médicas crónicas (20%) (Egede *et al.,* 2007; NICE 2009), con dolor crónico (Bair *et al.,* 2003) así como en pacientes con enfermedad física discapacitante (NICE 2009).

La mayoría de los casos la depresión se asocia a otro trastorno psiquiátrico co-mórbido (Kessler *et al.,* 2003). Según los resultados de la National Comorbidity Survey- Replication (NCS-R), realizada en Estados Unidos durante el 2001-2002, basada en criterios diagnósticos DSM-IV, el 72% de los pacientes con depresión a lo largo de la vida también cumplieron criterios de al menos otro trastorno DSM-IV (Kessler *et al.,* 2003). Los trastornos de ansiedad aparecen muy frecuentemente co-mórbidos con la depresión, pudiendo estar presente del 40 al 60% de los casos (Kessler *et al.,* 2003; Romera *et al.,* 2010; Gabilondo *et al*., 2010) [Tabla 2].

Tabla 2: Co-morbilidad de la depresión con otros trastornos mentales en España según el proyecto ESEMeD (N=247)

Trastorno co-mórbido	Prevalencia-año % (SE)
Cualquier trastorno	44,8 (6,0)
Cualquier trastorno de ansiedad	42,4 (5,1)
Distimia	27,1 (3,6)
Ansiedad generalizada	15,0 (2,9)

ESEMeD= European Study of the Epidemiology of Mental Disorders. SE= Standard error. Gabilondo *et al*., 2010

Cabe reseñar el mayor riesgo de los pacientes con depresión de desarrollar diversas enfermedades médicas, como la diabetes y las enfermedades cardiovasculares (Prince *et al*., 2007; Campayo *et al*., 2010; Kupfer *et al.,* 2012). De forma que, se ha encontrado que la depresión es un factor de riesgo independiente para la diabetes, incrementando el riesgo de la misma en torno a un 60% (Mezuk *et al.,* 2008; Campayo *et al.,* 2010). También se ha visto de manera consistente que la depresión supone un factor de riesgo para el accidente cerebro-vascular (Prince *et al.,* 2007) y aumenta significativamente el riesgo de recurrencia de infarto agudo de miocardio, así como la mortalidad en pacientes con coronariopatía (Hemingway *et al.,* 1999; Kuper *et al.,* 2002; Lespérance *et al.,* 2002; Glassman *et al.,* 2009).

Por último, señalar que la depresión es un factor de riesgo importante de suicidio. El riesgo de muerte a lo largo de la vida por suicidio en pacientes con trastorno depresivo mayor que han sido hospitalizados se ha comunicado clásicamente en torno al 15% (Guze *et al.,* 1970). Aunque estimaciones posteriores sitúan esta cifra en torno al 3.4% (Blair-West *et al.,*1991), independientemente de la cifra exacta no cabe duda del riesgo de suicidio asociado a la depresión, el cual se ha visto incrementado por la presencia de abuso de sustancias, trastorno de personalidad del grupo B, ser hombre y tener menor edad (Dumais *et al.,* 2005).

Por tanto, siendo la depresión un trastorno mental frecuente, un factor de riesgo de enfermedades médicas, factor de mal pronóstico de las mismas y un factor de riesgo de suicidio, constituye una entidad de suma importancia en nuestro medio, siendo necesario abordarla de manera óptima.

TRASTORNO DEPRESIVO MAYOR: IMPACTO DE LA ENFERMEDAD

El impacto de la depresión sobre el funcionamiento social y ocupacional así como sobre la salud física y la mortalidad es sustancial. La depresión puede producir un

mayor deterioro en el estado de salud que otras patologías crónicas, como la diabetes, la angina, la artrosis o el asma. De hecho, la co-morbilidad de la depresión con estas patologías crónicas produjo la mayor disminución en el estado de salud (Moussavi *et al.,* 2007).

La depresión se asocia generalmente a una alteración importante de la funcionalidad del paciente en el ámbito familiar, social y laboral (Kessler *et al.,* 2003; Lepine *et al.,* 1997; García-Campayo *et al.,* 2008). Tanto es así, que en el 59 % de los casos puede existir una discapacidad severa o muy severa encontrándose una clara relación directa entre la gravedad de la enfermedad y el grado de discapacidad (Kessler *et al.,* 2003).

Los efectos emocionales, motivacionales y cognitivos de la depresión reducen sustancialmente la capacidad de la persona para trabajar de manera efectiva, asociándose a pérdidas significativas en el ámbito laboral. Se ha comunicado una pérdida media por paciente de 20 días de trabajo en un periodo de 6 meses (Tylee *et al.*, 1999) o de 35 días en un periodo de un año (Kessler *et al.,* 2003). Estas cifras son incluso mayores que para la mayoría de las enfermedades médicas crónicas (Kessler *et al.,* 2001).

El coste total de la depresión en Europa se ha estimado en 118 billones de euros, y la mayor parte de esta cifra (61%) se debe a los costes indirectos referidos a las bajas por enfermedad y pérdidas de productividad (Valladares *et al.,* 2009). Un estudio recientemente realizado en Cataluña, mostró que el coste total anual de la depresión en Cataluña para 2006 fue de 735,4 millones de euros. De esta cifra, el 21,2% correspondió a costes directos y el 78,8% a los costes indirectos debido a la pérdida de productividad (Salvador-Carulla *et al.,* 2011).

Las consecuencia sociales y familiares incluyen una mayor dependencia de la asistencia social y beneficios sociales, con la consiguiente pérdida de la autoestima y la confianza en uno mismo; deficiencias en el ámbito social y familiar, incluyendo la disminución de la capacidad para relacionarse adecuadamente durante la enfermedad, pudiéndose cronificar a largo plazo, especialmente en aquellos pacientes con depresión con un curso crónico o recurrentes (NICE, 2010).

Según la OMS, en las edades comprendidas de 15 a 44 años, la depresión es la segunda causa de discapacidad, expresado en DALYs (Disability Adjusted Life Years), en años de vida saludable perdidos. Para el año 2020, según la OMS, la depresión se situaría en el segundo lugar de la clasificación de causas de discapacidad (DALYs) para todas las edades. Para el año 2030, la depresión pasaría a ser la primera causa de discapacidad en los países industrializados [Tabla 3]

Tabla 3: Causas principales de discapacidad (DALYs)

Ranking	2002	Previsión 2030 (nivel mundial)	Previsión para el 2030 (países con una alta renta per cápita)
1	Patologías perinatales	VIH/SIDA	Depresión
2	Infecciones respiratorias	Depresión	Patología isquémica coronaria
3	VIH/SIDA	Patología isquémica coronaria	Alzheimer y otras demencias
4	Depresión	Accidentes de tráfico	Trastornos por abuso de alcohol

DALYs: Disability Adjusted Life Years. Mathers *et al.*, 2006

TRASTORNO DEPRESIVO MAYOR: CRITERIOS DIAGNÓSTICOS

Los criterios diagnósticos operativos del DSM-IV-TR (Diagnostic and statistical manual of mental disorders- fourth edition-text revisión) para definir el episodio depresivo mayor son ampliamente utilizados, tanto a nivel clínico como a nivel de investigación.

La característica fundamental de un episodio depresivo mayor según el DSM-IV-TR es un estado de ánimo deprimido o una pérdida de interés o placer en las actividades usuales que persiste durante un período de al menos 2 semanas y se acompaña de una constelación de síntomas depresivos, tales como cambios en los patrones de comer o dormir, fatiga, dificultad para concentrarse, indecisión, pensamientos de muerte o suicidio, sentimientos de inutilidad, desamparo o desesperanza [Tabla 4]. Estos síntomas, no pueden ser atribuibles a duelo o a otro trastorno, como una condición inducida por una sustancia o una enfermedad médica (American Psychiatric Association, 2000). Aunque no sean una parte de los criterios del DSM-IV-TR, la ansiedad y los síntomas somáticos (en particular, musculares, respiratorios y genitourinarios) también pueden verse en el contexto de un trastorno depresivo mayor (Perlis *et al.,* 2006).

Tabla 4: Síntomas depresivos según los criterios diagnósticos DSM-IV-TR
Cinco (o más) de los síntomas siguientes durante el mismo período de 2 semanas y representan un cambio respecto del desempeño previo; por lo menos uno de los síntomas es estado de ánimo depresivo o pérdida de interés o placer.
Estado de ánimo depresivo la mayor parte del día, casi todos los días, indicado por el relato subjetivo o por observación de otros.
Marcada disminución del interés o del placer en todas, o casi todas, las actividades durante la mayor parte del día, casi todos los días.
Pérdida significativa de peso sin estar a dieta o aumento significativo, o disminución o aumento del apetito casi todos los días.
Insomnio o hipersomnia casi todos los días.
Agitación o retraso psicomotores casi todos los días.
Fatiga o pérdida de energía casi todos los días.
Sentimientos de desvalorización o de culpa excesiva o inapropiada (que pueden ser delirantes) casi todos los días (no simplemente autorreproches o culpa por estar enfermo).
Menor capacidad de pensar o concentrarse, o indecisión casi todos los días (indicada por el relato subjetivo o por observación de otros).
Pensamientos recurrentes de muerte (no sólo temor de morir), ideación suicida recurrente sin plan específico o un intento de suicidio o un plan de suicidio específico.

Es importante tener en cuenta que los síntomas deben representar un cambio para la persona respecto al desempeño previo. Es decir, se asocian a una alteración significativa de la funcionalidad habitual del paciente a nivel, laboral social o de otras esferas importantes. De hecho, la alteración de la funcionalidad presente en el paciente con depresión se equipara e incluso excede a la observada en muchas enfermedades crónicas (Greer *et al.*, 2010).

Otro de los criterios diagnósticos operativos utilizados es en base a la CIE-10 (clasificación internacional de enfermedades- décima versión). Según la CIE-10, en una lista de 10 síntomas depresivos, siempre deben estar presentes al menos dos de los tres síntomas considerados típicos de la depresión: ánimo deprimido, pérdida de interés y capacidad para disfrutar y aumento de la fatiga y el episodio debe durar al menos dos semanas. A pesar de las limitaciones de estos criterios operativos, estos permiten la homogenización del diagnóstico entre los distintos profesionales del ámbito clínico así como en la investigación.

Cabe reseñar que actualmente se está trabajando en los nuevos criterios diagnósticos, tanto por parte de la CIE como por el DSM. Aunque no sin dificultades, se están haciendo esfuerzos para intentar que ambas clasificaciones sean consistentes, existiendo un grupo de armonización. Discusiones conjuntas hacen referencia a la existencia de grandes clusters diagnósticos, la separación de los aspectos funcionales de los diagnósticos y sobre cómo la discapacidad relacionada con los trastornos mentales debe ser evaluada como un constructo separado. Uno de los esfuerzos del DSM a se centra en adoptar o crear medidas de deterioro que sean relativamente independientes de cada diagnóstico (World Health Organization Department of Mental Health and Substance Abuse).

Aunque la depresión ha sido clásicamente considerada como un trastorno de tiempo limitado, con una duración promedio de 4 a 6 meses y con una recuperación completa, cada vez parece quedar más claro que la recuperación incompleta y la recaída es lo habitual. El estudio de trastornos mentales realizado por la OMS en 14 centros de todo el mundo, encontró que tras un año, el 50% de los pacientes todavía tenía un diagnóstico de depresión (Simon *et al.,* 2002). Al menos el 50% de las personas, a raíz de su primer episodio de depresión mayor, pasarán a tener por lo menos un episodio más (Kupfer *et al.,* 1991) y después del segundo y tercer episodio, el riesgo de recaída se eleva a un 70 y 90%, respectivamente (Kupfer *et al.,* 1991). Por tanto, actualmente cada vez más se conceptualiza a la depresión como una enfermedad crónica.

REMISIÓN EN EL TRASTORNO DEPRESIVO MAYOR

CONCEPTUALIZACIÓN

En los últimos años la evidencia procedente de numerosos estudios clínicos ha demostrado que el objetivo óptimo en el tratamiento de la depresión es la remisión. A pesar de que hay consenso en cuanto a lograr este objetivo terapéutico, no hay una definición precisa y estandarizada sobre lo que significa "remisión" en depresión (Keller, 2003).

En 1991, Frank y colaboradores, propusieron crear criterios uniformes para facilitar la comparabilidad entre ensayos clínicos y la comunicación entre los médicos. En ese momento se definió remisión cuando el paciente no cumple criterios de depresión, está libre de síntomas o estos son mínimos (Frank *et al.,* 1991). De forma que esta definición de Frank y colaboradores se considera la definición clásica de remisión.

Remisión indicaría un nivel de mejoría tal que el paciente no se diferenciaría de otro sin depresión (Thase *et al.*, 2002). Cabe señalar que "remisión" es un término comúnmente usado en oncología y describe una ausencia completa de actividad de la enfermedad sin células neoplásicas. Aunque sería esperable y deseable que un paciente con depresión en remisión tuviese una "ausencia completa de la actividad de la enfermedad", el nivel de conocimiento actual de la fisiopatología de la depresión no nos permite llegar a esta afirmación.

El termino remisión también se ha equiparado a presencia de "salud" (Keller, 2003). Al igual que en otras enfermedades médicas crónicas, el nivel de salud en depresión debería ser evaluado teniendo en cuenta la combinación de tres dominios clave: síntomas, estado funcional y cambios fisiopatológicos (Keller, 2003). Dado las limitaciones actuales sobre la valoración de los cambios fisiopatológicos, se propone

que la mejor aproximación para la definición de remisión, sería un sistema que primeramente tenga en cuenta los síntomas pero también tenga en cuenta el funcionamiento psicosocial del paciente. Es decir, el resultado óptimo del tratamiento sería la remisión con ausencia de síntomas y ausencia de alteración funcional, o restablecimiento de una funcionalidad completa y saludable. Remisión sería un marcador de salud. En un futuro, a medida que el conocimiento sobre la fisiopatología de la depresión evolucione, la definición de remisión avanzará y podrá indicar la ausencia verdadera de enfermedad o actividad (Keller, 2003).

Según el DSM-IV-TR se define remisión total cuando "durante los últimos dos meses no ha habido signos o síntomas significativos de la alteración". Es decir, se define remisión teniendo en cuenta únicamente la resolución de los síntomas independientemente de los aspectos funcionales. Cabe reseñar que para el diagnóstico de un episodio de depresión, según los criterios diagnósticos DSM-IV-TR, es necesario la presencia de una alteración de la funcionalidad del paciente, laboral social o de otras áreas importantes de la actividad del individuo. Por lo tanto, aunque los aspectos funcionales sí que son importantes a la hora del diagnóstico según el DSM-IV-TR, estos no quedan recogidos en la definición de remisión.

En el 2006 se publicaron las recomendaciones sobre remisión del grupo de trabajo de la American College of Neuropsychopharmacology (ACNP) (Rush et al., 2006). Según estas recomendaciones el concepto de remisión implicaría que los signos y síntomas de la enfermedad deben de estar ausentes o prácticamente ausentes. La remisión se asocia típicamente con una vuelta a la función diaria previa al comienzo de la enfermedad. Como aspecto novedoso respecto a otras conceptualizaciones, según la ACNP, remisión se refiere únicamente a los 9 síntomas nucleares necesarios para el diagnóstico de un episodio de depresión en base al DSM-IV-TR. Más aún, se recomienda que en un estado de remisión ni la tristeza ni la anhedonia estén

presentes, así como menos de tres del resto de síntomas nucleares, durante un periodo mínimo de tres semanas. Este panel recoge que la función diaria no debería ser parte de la definición de remisión, ya que la remisión se asocia típicamente con una vuelta al nivel de funcionamiento previo al episodio. Por lo tanto, según este panel de expertos, la funcionalidad debería evaluarse como un resultado secundario.

EVALUACIÓN DE LA REMISIÓN: CRITERIOS OPERACIONALES

En 1991 Frank y colaboradores, propusieron criterios operacionales para la definición de remisión basados en puntuaciones en escalas de valoración de la sintomatología estandarizadas (Tabla 5).

Tabla 5: Remisión: Criterios operacionales propuestos por Frank et al. 1991

Asintomático	HAMD17 ≤ 7	BDI ≤ 8	SADS≤ 2 Síntomas
Remisión completa	≥2 semanas < 6 meses asintomático	≥3 semanas < 4 meses asintomático	≥2 semanas < 8 semanas asintomático

Cabe señalar que todavía no existe consenso sobre cuál es la mejor forma de medir la remisión. Actualmente, los criterios operacionales que definen remisión usados en los ensayos clínicos se basan fundamentalmente en puntuaciones en escalas sintomáticas. Aunque puede existir cierta variabilidad y controversia en cuanto a los puntos de corte escogidos, los más utilizados se presentan en la tabla 6.

Tabla 6: Remisión: Criterios operacionales		
Escala	Punto de corte para remision	Evaluador
HAMD-17	≤7	Clínico
MADRS	≤10	Clínico
CGI	=1	Clínico
QIDS-C/ QIDS-SR	≤5	Clínico/Paciente
PHQ-9	≤4	Paciente
Keller MB. 2003; Trivedi MH. 2009		

La escala HAMD- 17 se ha usado ampliamente y actualmente se considera el "gold standard" (Moller, 2008). El criterio para definir remisión más comúnmente utilizado es un punto de corte menor o igual a 7. Este punto distingue de forma fiable a los pacientes que tienen y no tienen depresión (Thase *et al.,* 2002). La puntuación media de un paciente con depresión ambulatoria se sitúa típicamente entre 18 y 22. Teniendo en cuenta la distribución normal de las puntuaciones, sería muy improbable que un paciente con una puntuación de 7 o menos cumpliese criterios de depresión mayor. De igual forma, la mayoría de los individuos no deprimidos, "sanos", puntúan entre 1 y 3, por lo que sería muy improbable que alguien que puntúe 8 o más estuviese "bien" (Thase *et al.*, 2002).

La escala HAMD-17, aunque sigue siendo el "gold standard", ha sido criticada ya que no incluye los 9 criterios diagnósticos de depresión según el DSM-IV, por el gran peso que tienen los síntomas somáticos y por su multidimensionalidad. Aunque la multidimensionalidad es importante para cubrir un amplio rango de síntomas, puede llevar a error cuando se mide severidad y respuesta al tratamiento, por lo que algunos autores proponer el uso de escalas unidimensionales (Ruhé *et al.,* 2005).

Recientemente se han introducido nuevas escalas más cortas que representan en muchos casos formas abreviadas de las ya existentes. Un ejemplo es la escala de Hamilton de depresión de 7 items, donde una puntuación ≤ 3 correspondería a una puntuación ≤ a 7 en la HAMD-17 (McIntryre *et al.,* 2002). En la escala de 5 items de Bech, procedente de la escala de HAMD-17, que representa los síntomas nucleares de la depresión (items 1, 2, 7, 8, 10 y 13), una puntuación ≤ a 4 correspondería a una puntuación ≤ a 7 en la HAMD-17 (Ruhé *et al*., 2005). La sub-escala de Maier (ítems 1, 2, 7-10 de la HAMD-17) también representa los síntomas nucleares de la depresión. A diferencia de la escala Bech, la sub-escala de Maier incluye agitación y no incluye los síntomas somáticos generales. Una puntuación ≤ a 4 se corresponde con una puntuación ≤ a 7 en la HAMD-17 (Ruhé *et al.,* 2005). Ambas escalas, al ser unidimensionales, harían frente al problema de la multidimensionalidad de la HAMD-17.

La PHQ-9 es un cuestionario auto-aplicado por el paciente que incluye los nueve criterios diagnósticos de la depresión mayor. Al igual que los instrumentos anteriores es rápido de aplicar, por lo que tendría la ventaja de poder usarse en la práctica clínica de forma rutinaria (Kroenke *et al.,* 2001)

Cabe destacar que las escalas recomendadas por la ACNP para evaluar la remisión son aquellas que incluyan los 9 síntomas nucleares usados para el diagnóstico de un episodio de depresión mayor (Patient Health Questionnaire; 16 item-Quick Inventory of Depressive Symptomatology- Clinician Rating; 16 item-Quick Inventory of Depressive Symptomatology- Self-report). Escalas ampliamente usadas como la HAMD-17 y la MADRS no cumplirían este criterio. Si la definición de remisión propuesta por la ACNP es aceptada, no sería suficiente una mera puntuación total de la escala para declarar a un paciente en remisión, debiendo comprobar la ausencia de anhedonia y tristeza.

Aunque no cabe duda que estos criterios operacionales son útiles para valorar la actividad de la enfermedad y los resultados de los tratamientos, desafortunadamente no están libres de limitaciones como marcadores del estado de remisión. Se basan únicamente en aspectos sintomáticos, sin incluir entre otros, aspectos funcionales y fisiopatológicos. Asimismo, se ha cuestionado su utilidad clínica, especialmente cuando los instrumentos requieren tiempo para su correcta aplicación. Aun así, la existencia de criterios e instrumentos encaminados a facilitar la evaluación del curso de la enfermedad es un paso necesario hasta que el mejor conocimiento de la enfermedad nos permita tener marcadores biológicos indicativos de un estado de remisión.

SÍNTOMAS RESIDUALES: DEFINICIÓN Y CARACTERIZACIÓN

Un número considerable de pacientes a pesar de responder al tratamiento, típicamente definido como una mejora de más del 50% en una escala sintomática, no alcanzan un estado de remisión, presentando síntomas residuales (Kennedy *et al.*, 2007). Esta situación ya se contempló por la fundación MacArthur cuando a principios de los noventa revisó la terminología sobre el curso evolutivo del TDM (Frank *et al.,* 1991). Entonces, se definió remisión parcial cuando tras el tratamiento agudo el paciente presenta síntomas depresivos pero no son de la suficiente magnitud para cumplir criterios de TDM. De igual modo, el DSM-IV define a los síntomas residuales como la presencia de algunos síntomas del episodio depresivo mayor que no son suficientes para cumplir criterios del episodio. Actualmente, según el ICD no existe una definición de los síntomas residuales.

Cabe reseñar que para el conocimiento de los síntomas residuales, la mayoría de los estudios no están diseñados específicamente para su evaluación, por lo tanto, no incluyen instrumentos específicos. Esto limita la caracterización de los síntomas

residuales a escalas como la HAMD-17, o la QIDS, dejando de lado, entre otros, los síntomas residuales cognitivos (Iglesias *et al.,* 2009)

Paykel y colaboradores (Paykel *et al.,* 1995), fueron de los primeros en estudiar los síntomas residuales en el TDM. Se consideró la presencia de síntomas residuales tras la remisión parcial en aquellos pacientes que tras el tratamiento agudo, no presentaban criterios de episodio y tenían una puntuación en la HAMD-17 entre 8 y 18. Un 32% de los pacientes presentaban síntomas residuales. El patrón de síntomas encontrado fue de típicos síntomas depresivos (tristeza, culpa, anhedonia, ansiedad psiquica) pero de intensidad leve, siendo menos frecuentes los síntomas biológicos como retardo, pérdida de peso e insomnio.

Estudios posteriores, realizados en muestras no hospitalarias, han encontrado una mayor prevalencia y un distinto patrón de síntomas residuales al encontrado por Paykel. En el estudio STAR*D se evaluó a los pacientes con TDM que respondieron (reducción del 50% o más en la puntuación del QIDS-SR_{16}) a 12 semanas de tratamiento con citalopram sin alcanzar la remisión (QIDS-SR_{16} < 6) (McClintock *et al.,* 2011). La mayoría de estos pacientes presentaban síntomas residuales. Los dominios sintomáticos más frecuentes fueron el insomnio (94.6%), la tristeza (70.8%) y la disminución de la concentración (69.6%) (McClintock *et al.,* 2011).
Taylor y colaboradores, evaluaron en un grupo de pacientes con depresión qué síntomas depresivos persistían tras la respuesta al tratamiento cognitivo agudo (Taylor *et al.,* 2010). Tras completar 20 sesiones de terapia cognitiva, un considerable porcentaje de respondedores presentaban ansiedad somática (42%), ansiedad psicológica (37%), insomnio medio (36%), tristeza (29%), disminución del libido (29%), insomnio tardío (24%), anergia (21%), sentimientos de culpa (18%), insomnio

temprano (17%) y anhedonia (14%), evaluados mediante la HAMD- 17 (Taylor *et al.*, 2010).

Los resultados derivados de estos estudios sugieren que los pacientes que responden al tratamiento antidepresivo, pero no alcanzan la remisión, presentan frecuentemente síntomas residuales, siendo amplio y variable el rango y tipo de síntomas residuales.

FACTORES PREDICTIVOS DE SÍNTOMAS RESIDUALES

En cuanto a los factores que se han encontrado asociados a un mayor riesgo de síntomas residuales, la severidad inicial del episodio y la presencia de trastornos de personalidad, fueron factores de riesgo (Paykel *et al.,* 1995). Esto no fue así para una mayor duración del episodio, distima previa, uso de dosis menores antidepresivas durante el episodio, ni para un mayor número de episodios previos (Paykel *et al.,* 1995). Otros estudios han encontrado un mayor riesgo en pacientes mayores, en presencia de trastornos del eje II y con historia previa de abuso de alcohol o drogas (Kennedy *et al.,* 2005).

SÍNTOMAS RESIDUALES Y SU PERSISTENCIA EN EL TIEMPO

Para algunos pacientes estos síntomas residuales pueden tener un curso transitorio, pero sin embargo, para otros pueden persistir a pesar del tratamiento. La evidencia procedente de estudios epidemiológicos muestra que muchos pacientes con TDM tienen síntomas residuales que persisten incluso después de un año tras la resolución del episodio (Mojtabai, 2001; Judd *et al.,* 1998). Judd y colaboradores, siguieron prospectivamente a una cohorte de 431 pacientes con TDM durante 12 años. La presencia de síntomas residuales fue la fase más frecuente de la enfermedad. De forma que el 43% del tiempo del seguimiento los pacientes tenían síntomas residuales. Los pacientes presentaron criterios de TDM durante el 15% de las semanas de seguimiento y estuvieron en remisión el 41% del tiempo (Judd *et al.,* 1998). De forma similar, Kennedy y colaboradores, en un estudio de 10 años de seguimiento, encontró

que los pacientes presentaban más periodos con síntomas residuales que con criterios de depresión mayor (Kennedy *et al*., 2004). En un estudio reciente de seguimiento a tres años, de 267 pacientes con un episodio de depresión, mostró que los problemas cognitivos, falta de energía y los problemas de sueño estaban presentes el 39-44% del tiempo durante los periodos de remisión parcial (Ormel *et al.,* 2010).

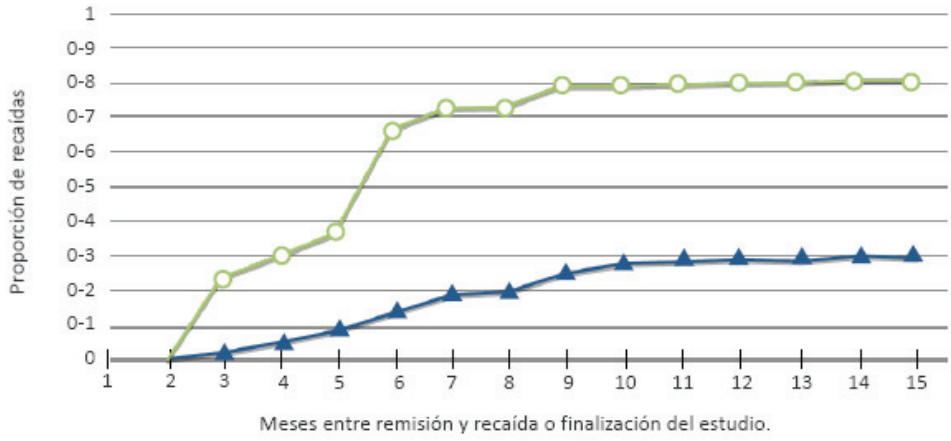
Por tanto, estos estudios indican que la presencia de síntomas residuales tras el episodio agudo no sólo es una entidad frecuente si no también, en muchas ocasiones persisten en el tiempo.

REMISIÓN COMO OBJETIVO TERAPÉUTICO Y SU VALOR PRONÓSTICO

La evidencia procedente de numerosos estudios clínicos ha demostrado que la remisión es el objetivo terapéutico óptimo ya que se asocia a un mejor pronóstico en comparación con una respuesta sin remisión por tanto persistencia de síntomas residuales.

En un estudio observacional de 15 meses de duración, llevado a cabo por Paykel y colaboradores, se mostró que aquellos pacientes que respondían al tratamiento farmacológico (tricíclicos o ISRS) pero no alcanzaban la remisión (HAMD-17 menor de 18 y mayor de 7) tenían tres veces más riesgo de recaer que aquellos que sí remitían (HAMD-17 menor o igual a 7); 76 % vs. 25% respectivamente (Paykel *et al.,* 1995).

Figura 1: Persistencia de síntomas residuales y mayor riesgo de recaída



Proporción de pacientes con (▲) y sin (○) síntomas residuales que recaen.

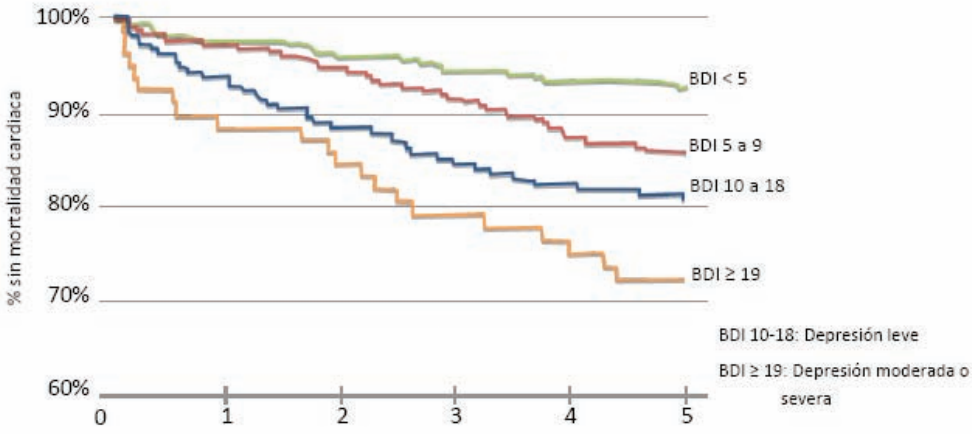
Paykel *et al.*, 1995

Este aumento del riesgo de recaída asociado a la ausencia de remisión ha sido replicado posteriormente por varios estudios (Simon *et al.,* 2000; Pintor *et al.,* 2003; Pintor *et al*., 2004; Judd *et al*., 1998; Judd *et al.,* 2000). Simon y colaboradores, realizaron un estudio prospectivo de dos años de seguimiento en atención primaria. Observaron que aquellos pacientes que tras tres meses de tratamiento habían respondido tenían casi tres veces más riesgo de recaer o de recurrir que aquellos que alcanzaron la remisión (Simon *et al*., 2000). Más recientemente, un estudio realizado en España encontró que los pacientes con depresión que respondían sin remitir tenían un 92% de probabilidad de recaer a los 4 años de seguimiento, en comparación con un 50 % de riesgo en los pacientes que remitían (Pintor *et al*., 2004). Cabe destacar el estudio realizado por Judd y colaboradores de 12 años de seguimiento, donde se compararon los pacientes que remitieron y los que respondieron con síntomas residuales teniendo en cuenta el número de episodios depresivos previos. De forma llamativa, aunque la historia de episodios depresivos previos se asociaba a un mayor riesgo de recurrencia (OR = 1.6), la presencia de síntomas residuales fue el factor de riesgo más importante (OR = 3.6) de recurrencia (Judd *et al.,* 1998).

No alcanzar la remisión también se ha visto asociado a consecuencias a más largo plazo, como un mayor riesgo de cronicidad, recaídas más tempranas, así como periodos libres de síntomas más cortos (Judd *et al.,* 2000).

La presencia de síntomas residuales no sólamente empeora el pronóstico de la depresión, también puede empeorar el pronóstico de las enfermedades médicas co-mórbidas. La presencia de síntomas depresivos se ha asociado a un incremento del riesgo de accidente cerebrovascular y aumento de la morbi-mortalidad tras un infarto agudo de miocardio (Kennedy *et al.,* 2005). En este sentido, en un estudio realizado en pacientes con infarto agudo de miocardio se encontró una asociación entre la presencia de síntomas depresivos y una mayor mortalidad (Figura 2). De forma que en pacientes con una BDI en incluso rangos normales (BDI<10), la mortalidad fue mayor en aquellos pacientes con más síntomas depresivos (BDI= 5-9) en comparación con aquellos con menos síntomas (BDI< 5) depresivos (Lespérance *et al.,* 2002). En un estudio más reciente, que siguió durante 7 años a una cohorte de pacientes con depresión y síndrome coronario agudo, aquellos paciente que no remitieron tras seis meses de tratamiento (CGI= 3-7) tuvieron más del doble de riego de mortalidad en comparación con aquellos que alzaron la remisión (CGI= 1-2) (Glassman *et al*., 2009).

Figura 2: Supervivencia tras un IAM en relación con la presencia de síntomas depresivos y depresión (BDI) durante la hospitalización



BDI: Beck Depression Inventory

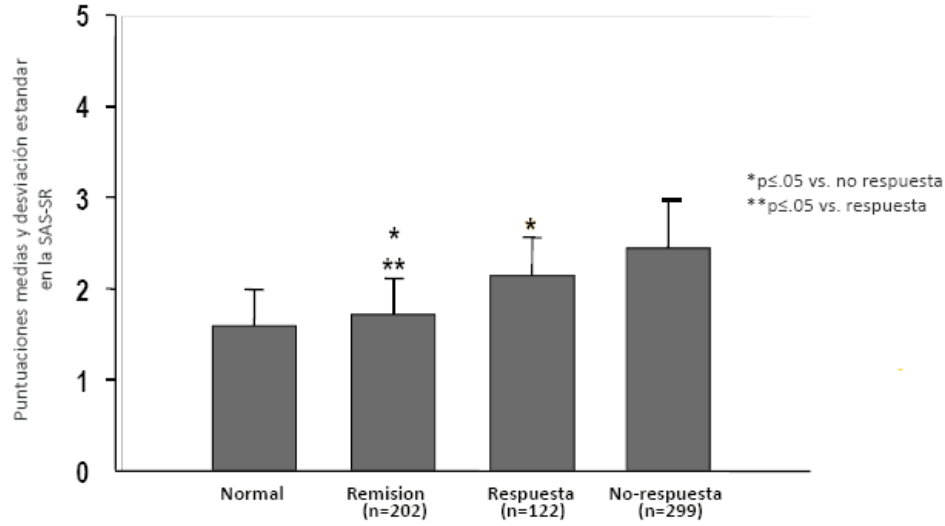
IAM: Infarto agudo de Miocardio

Lesperance *et al.*, 2002.

La presencia de síntomas residuales se ha visto que se asocia a una alteración significativa de la funcionalidad del paciente, tanto a nivel general como en el ámbito laboral, familiar y social (Miller *et al*., 1998; Simon *et al.,* 2000; Trivedi *et al.,* 2009). Miller y colaboradores, en el contexto de un ensayo clínico de 12 semanas de duración, evaluaron la mejoría funcional tras el tratamiento agudo. Únicamente los pacientes que alcanzaron la remisión tenían niveles de funcionamiento psicosocial que se acercaban o igualaban a una muestra control sin depresión. La funcionalidad global, laboral, social y en otras áreas relevantes estaba significativamente alterada en aquellos pacientes que respondieron pero presentaban síntomas residuales (Figura 3). De hecho, la disfunción en alguna de las áreas era similar al grupo de pacientes no respondedores (Miller *et al.,* 1998). En un estudio más reciente, a partir de los datos de un ensayo clínico randomizado, los pacientes que lograron la remisión sintomática completa experimentaron mayores mejoras funcionales que los que respondieron pero no alcanzaron la remisión (Trivedi *et al.,* 2009). En términos específicos de funcional laboral, en un análisis secundario procedente de un ensayo clínico randomizado de dos años de duración, los pacientes que tras un año de tratamiento remitieron tenían

más probabilidad de mantener el empleo remunerado y reportaron menos días perdidos de trabajo que aquellos que mejoraron sin remitir (Simon *et al.,* 2000).

Figura 3: Mejoría funcional tras el tratamiento agudo en función del nivel de respuesta



SAS-SR: Social adjusment scale- self reported

Miller *et al.*,1998

Por último cabría reseñar que la presencia de síntomas residuales se asocia a un mayor riesgo de suicidio. En un estudio que siguió durante 18 meses a 542 pacientes con TDM, se observó que el riesgo relativo de intento de suicidio fue 2.5 veces mayor en los pacientes en remisión parcial en comparación con los pacientes en remisión completa (Sokero *et al.,* 2005).

En cuanto al riesgo de recaída asociado a los síntomas residuales en pacientes que han remitido los resultados hasta la fecha son escasos y no son claros. Hay estudios que no han encontrado un mayor riesgo (Ioveno *et al.,* 2011; Bertschy *et al.,* 2010), sin embargo otros han comunicado un aumento de riesgo con un mayor número de síntomas residuales (Nierenberg *et al.,* 2010).

En resumen la presencia de síntomas residuales tras el tratamiento agudo se asocia a un aumento del riesgo de recaídas y recurrencias, recaídas más precoces, riesgo de

cronicidad, empeoramiento del curso de las enfermedades médicas co-mórbidas, alteración de la funcionalidad del paciente y aumento del riesgo de suicidio. Por lo tanto, las implicaciones pronósticas derivadas de no alcanzar la remisión, de la persistencia de síntomas residuales, son múltiples. Ante estos datos, se hace indispensable realizar un abordaje y tratamiento de la depresión óptimo, encaminado a lograr la remisión del episodio.

REMISIÓN Y FUNCIONALIDAD EN EL TRASTORNO DEPRESIVO MAYOR

FUNCIONALIDAD: CONCEPTUALIZACIÓN

La remisión del episodio depresivo conceptualmente implica una recuperación del nivel de funcionamiento existente previamente al inicio del episodio (Keller, 2003). Pero, ¿qué entendemos por funcionalidad o funcionamiento? Este es un concepto amplio, que cubre diferentes dominios. Áreas comúnmente incluidas en el concepto de funcionalidad son, funcionalidad laboral (la habilidad de llevar a cabo tareas y actividades asociadas al trabajo), cuidado personal, funcionalidad social (relaciones personales), familiar y cognitiva. Una definición aceptada del término funcionalidad es "la capacidad de realizar actividades o tareas en el modo en el que se espera o se requiere" (Endicott *et al*., 2010). De esta forma, funcionalidad social se ha definido como "la capacidad del individuo de realizar y llevar a cabo un papel social normal" (Hirschfeld *et al.,* 2000) o "la interacción del individuo con su entorno y la capacidad de llevar a cabo su papel dentro del mismo" (Bosc *et al.,* 1997).

Cabe reseñar que el término funcionalidad a veces se confunde con otros cómo satisfacción o calidad de vida. Funcionalidad, así como satisfacción se consideran componentes de la calidad de vida. Sin embargo funcionalidad y satisfacción pueden variar de forma independiente, por ejemplo un paciente puede tener alteración de la funcionalidad en diferentes dominios y estar satisfecho con su situación en la vida. Más aun, la satisfacción es subjetiva y por tanto valorada por el paciente y la funcionalidad puede ser medida de una forma más objetiva (Endicott *et al.*, 2010).

MEDICIÓN DE LA FUNCIONALIDAD: INSTRUMENTOS DE EVALUACIÓN

Existen numerosos instrumentos validados que se usan comúnmente en estudios clínicos para valorar la funcionalidad en pacientes con depresión (Tabla 7).

Una de las escalas más utilizadas, tanto en estudios en depresión como en ansiedad, es la escala de discapacidad de Sheehan (Sheehan Disability Scale; SDS). Incluye tres área funcionales; trabajo-estudios, social y familiar. Los pacientes puntúan en una escala de cero a diez en qué medida los síntomas han interferido en cada uno de estos dominios (Sheehan *et al.,* 1996). Se considera niveles normales de funcionalidad una puntuación total menor o igual a 6 (Sheehan *et al.,* 2011).

Otra escala comúnmente utilizada es la escala SOFAS (social and occupational functioning scale) también conocida como EEASL (escala de evaluación de la actividad social y laboral). Esta escala se deriva del DSM-IV-TR, el clínico o investigador indica el nivel de funcionamiento del individuo en un continuo de 1 a 100 (siendo 100 funcionalidad óptima). Mide puramente la alteración funcional sin tener en cuenta los síntomas (Goldman *et al.,* 1992).

Dentro de las escalas de evaluación de la funcionalidad, hay instrumentos considerados breves y sencillos de utilizar (GAF, SDS, SOFAS), así como otros más complejos que incluyen múltiples dominios (SAS). En la tabla 7 se recogen las características de varias de las escalas utilizadas para la valoración de la funcionalidad.

Tabla 7: Instrumentos de medición de la funcionalidad

Instrumento	Número de items	Dominios incluidos
SOFAS (social and occupational functioning scale)	Único	Social Laboral
Escala de discapacidad de Sheehan (Sheehan Disability Scale; SDS	3	Social y actividades de ocio Laboral(remunerado- estudiante-tareas del hogar) Relaciones con familia, role dentro de la familia
Escala de Ajuste Social Social Adjustment Scale (SAS)	48	Trabajo (remunerado, hogar, estudiante) Actividades de ocio y sociales Papel marital Papel parental Papel como un miembro en la familia
Escala de valoración global de la funcionalidad (Global assessment of functioning scale; GAF)	Único	Severidad de los síntomas y alteración funcional
WHODAS (World Health Organization Disability Assessment Schedule)	36	Cognición Mobilidad Autocuidado Interacciones interpersonales Actividades Participación en la sociedad
Escala de productividad laboral de Endicott	25	Eficiencia y productividad laboral
Longitudinal Interval Follow-up Evaluation-Range of Impaired Functioning Tool	9	Trabajo Relaciones Interpersonlales Satisfacción general con el funcionamiento Recreación
Life Functioning Questionnare	14	Tareas en el trabajo/escuela Tareas en el hogar Tiempo de ocio con familia Tiempo de ocio con amigos
Health of the Nation Outcomes Scales	12	Comportamiento Disfunción Síntomas Funcionamiento social

Endicott J et al. 2009

Aunque hay numerosas escalas para la evaluación de la funcionalidad, cabe mencionar que estas se emplean fundamentalmente en investigación, siendo escaso su empleo en la práctica clínica habitual. Es posible que esta práctica sea el reflejo del mayor peso que tradicionalmente han tenido los aspectos sintomáticos sobre los funcionales en el campo de la investigación en depresión.

Por último, uno de los aspectos fundamentales a considerar es la evaluación de la funcionalidad pre-mórbida, donde el uso de escalas queda limitado y la entrevista clínica es la herramienta con mayor peso. La evaluación de la funcionalidad pre-

mórbida cobra un papel relevante para establecer objetivos terapéuticos concretos y adaptados a cada paciente.

REMISIÓN SINTOMÁTICA Y RECUPERACIÓN FUNCIONAL COMO OBJETIVO TERAPÉUTICO.

Actualmente la remisión sintomática es el objetivo principal del tratamiento del episodio de depresión. Sin embargo, la recuperación de la funcionalidad al nivel pre-mórbido se identifica cada vez más como un objetivo significativo adicional a la remisión sintomática (Papakostas, 2009).

La recuperación de la funcionalidad se ha relacionado con un mejor pronóstico de la depresión. Estudios observacionales de seguimiento han encontrado una asociación significativa entre alteración de la funcionalidad y mayor duración de los episodios (Leon *et al.,* 1999). También se ha visto que la presencia de alteración en el funcionamiento, tras la recuperación del episodio, se relaciona con más recurrencias depresivas (Solomon *et al.,* 2004). Más recientemente, este mismo autor examinó la relación entre el funcionamiento psicosocial y la recuperación en una amplia muestra de pacientes con depresión mayor mediante un estudio observacional de 20 años de seguimiento. La recuperación se definió como al menos 8 semana consecutivas sin síntomas de depresión o únicamente uno o dos síntomas de intensidad leve. La alteración funcional se asoció de forma significativa con una menor probabilidad de recuperación del episodio de depresión mayor (Solomon *et al.,* 2008).

La recuperación funcional también es un objetivo clínico expresado por el paciente con depresión. Zimmerman (Zimmerman *et al.,* 2006) estudió qué factores definían la remisión del episodio desde el punto de vista del paciente. Para ello, preguntó a 535 pacientes con depresión sobre la importancia de 16 factores en determinar si la depresión estaba en remisión. La funcionalidad social y laboral, expresada como el

retorno al nivel normal de funcionamiento, fue un factor identificado como “muy importante” por el 74% de los pacientes. Incluso por encima de la ausencia de síntomas depresivos, donde el 70% de los pacientes lo consideraron como un factor “muy importante”. Pero además de la recuperación funcional, la presencia de salud mental positiva (optimismo y autoconfianza) y volver a sentirse como antes, como uno mismo, se identificaron como “muy importantes” por el paciente (Zimmerman *et al.,* 2006). Es decir, desde el punto de vista del paciente, dentro de sus expectativas de recuperación, la recuperación funcional se considera altamente relevante.

Tabla 8 : Factores determinantes de remisión según el paciente

Factores identificados como muy importantes por el paciente para determinar la **REMISIÓN**	% de pacientes (n=535)
Ausencia de síntomas de depresión	70,6%
Presencia de una salud mental positiva	77,3%
Vuelta a nivel nomal de funcionalidad en el trabajo, el hogar, el centro educativo	74,3%
Sentir un control de las emociones	71,9%
Buena funcionalidad	70,3%
Participar y disfrutar de las relaciones con familiares/amigos	70,7%
Sentirse como siempre, tener una vida normal	75,6%

Zimmerman *et al.,* 2006

DETERMINANTES DE LA RECUPERACIÓN FUNCIONAL

Pero, ¿cuáles son los determinantes de la mejoría o restauración funcional en los pacientes con depresión mayor? Los factores identificados que contribuyen incluyen entre otros; la trayectoria funcional del paciente a lo largo de la vida, la efectividad del tratamiento, el tiempo hasta la remisión, la duración de la remisión y la calidad de la remisión (Papakostas, 2009).

Tabla 9. Determinantes de la recuperación funcional
Trayectoria funcional del paciente a lo largo de la vida
Efectividad del tratamiento
Remisión completa de los síntomas depresivos
Tiempo hasta la remisión
Duración o mantenimiento de la remisión
Calidad o grado de la remisión
Papakostas, 2009

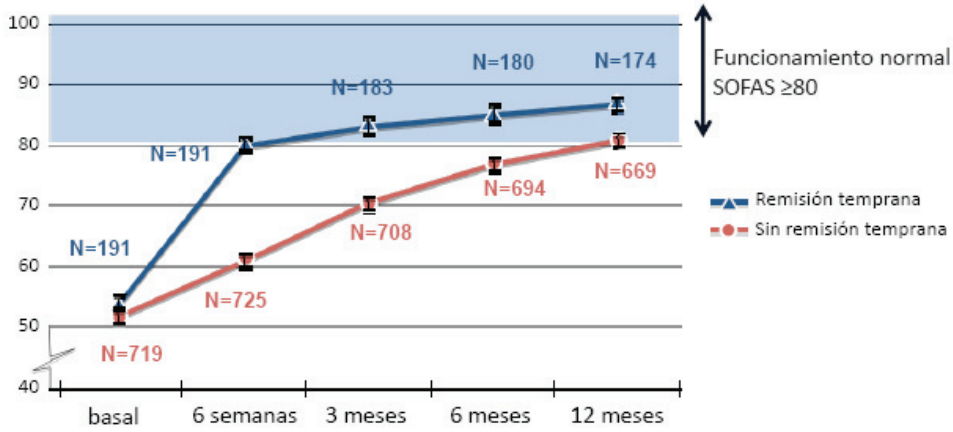
La funcionalidad pre-mórbida es un factor determinante en el nivel de funcionalidad después del episodio. Ormel y colaboradores (Ormel *et al.,* 2004), en un estudio prospectivo poblacional realizado en Holanda, examinaron la funcionalidad psicosocial antes, durante y después del primer episodio de depresión. Observaron que tras la remisión, la funcionalidad regresó a los niveles pre-mórbidos. La alteración funcional psicosocial reflejaba en gran parte la continuación de la alteración funcional pre-mórbida.

En relación con la efectividad del tratamiento se hace necesario una resolución completa y sostenida de los síntomas depresivos para alcanzar la restauración del funcionamiento. De forma que, aproximaciones terapéuticas efectivas, que lleven al mantenimiento de un estado de remisión sintomática, aumentarán las opciones de recuperación funcional del paciente (Papakostas, 2009). El estudio de Miller y colaboradores (Miller *et al*., 1998) evidenció esta relación. Aquellos pacientes que alcanzaron la remisión (HAMD-17≤7) tras 12 semanas de tratamiento agudo, presentaban mejor funcionalidad que aquellos que sólo respondieron. Asimismo, tuvieron niveles similares de funcionamiento que una población control sin depresión. En un estudio más reciente, Papakostas evaluó la funcionalidad en un grupo de pacientes con depresión que recibieron tratamiento con fluoxetina durante 8 semanas.

Al igual que en el estudio de Miller, la mejoría funcional fue mayor en aquellos pacientes que alcanzaron la remisión (HAMD-17≤7) vs. los que únicamente respondieron (reducción en la puntuación total del HAMD-17 mayor o igual al 50%) (Papakostas *et al.,* 2004).

Respecto al tiempo hasta la remisión, una respuesta más temprana así como una remisión temprana, se asoció significativamente a una mayor mejoría funcional (Papakostas *et al.,* 2004; Ciudad *et al.,* 2012). Cabe reseñar el estudio de Ciudad y colaboradores, recientemente realizado en España sobre una amplia muestra de pacientes con un episodio de depresión mayor seguidos durante 1 año. Este estudio evidenció que la respuesta temprana era el factor más fuertemente asociado a la mejoría funcional. Del mismo modo, la remisión temprana, dentro de las primeras 6 semanas de tratamiento, fue un factor fuertemente asociado a la mejoría funcional. En los pacientes con una remisión temprana, se observaron rangos normales de funcionamiento tan pronto como a las 6 semanas. Mientras que en aquellos que no alcanzaron la remisión temprana se requirió un año hasta alcanzar niveles normales de funcionamiento (Figura 4).

Figura 4: Evolución temporal de la funcionalidad (puntuación media SOFAS) en función de que el paciente presentara o no remisión temprana



Remisión temprana: No presentar criterios de TDM y una puntuación de HAM-D17 ≤ 7 en el transcurso de las 6 primeras semanas
SOFAS: Social and Occupational Functioning Scale

Ciudad *et al.*, 2012

La duración y el mantenimiento de la remisión son factores que también contribuyen a la restauración funcional. Furukawa y colaboradores (Furukawa *et al.,* 2001) encontraron que el funcionamiento mejoraba con la mejoría sintomática, pero sin embargo, no se alcanzaron niveles normales de funcionamiento hasta pasados unos meses de remisión sintomática. Es decir, estos resultados parecen indicar que la recuperación funcional va "retrasada" con respecto a la recuperación sintomática. Por otro lado, el mantenimiento de la remisión, evitar perder este estatus asintomático, también se hace imprescindible. La pérdida de la remisión no sólamente contribuye a un empeoramiento del funcionamiento sino también a un aumento del riesgo de recaída y de recurrencia, por tanto perdiéndose la recuperación funcional (Papakostas, 2009).

Por último, la calidad o grado de la remisión también se ha asociado a la recuperación funcional. Incluso en pacientes que están en remisión se han encontrado diferencias significativas en cuanto al grado de funcionamiento. Zimmerman y colaboradores observaron que los pacientes que puntuaban igual o menos de 2 en la HAMD-17 comunicaron menor disfunción psicosocial que aquellos con una puntuación entre 3 y 7 (Zimmerman *et al.,* 2005). Otro estudio encontró que puntuaciones en la HAMD-17 ≤ 6 predecía menores actitudes disfuncionales y un mayor funcionamiento global en comparación con puntuaciones entre 7 y 10 (Riso *et al.,* 1997). Se han encontrado resultados similares usando otros instrumentos como la escala de Montgomery-Asberg, donde pacientes con puntuaciones más bajas (puntuación total ≤4) comunicaron un mejor funcionamiento global en comparación con los pacientes con puntuaciones más altas (puntuación total= 5-9) (Zimmerman *et al*., 2004).

Por tanto, podemos concluir que dentro de los factores que determinan la recuperación funcional, la remisión de los síntomas es un factor clave. Pero no sólamente cobra relevancia alcanzar la remisión sintomática, sino que para maximizar las opciones de

recuperación funcional esta remisión tendría que producirse en un corto periodo de tiempo, tan pronto como fuera posible. Asimismo, la "calidad" o grado de remisión es un factor a tener en cuenta, ya que incluso en remisión, menores puntuaciones en las escalas sintomáticas se asocian a una mejor funcionalidad. Por último, esta remisión sintomática tiene que mantenerse en el tiempo para consolidar la recuperación funcional y disminuir el riesgo de recaída, por tanto disminuir el riesgo de pérdida funcional.

REMISIÓN Y FUNCIONALIDAD. ASPECTOS SIN RESOLVER

Remisión no sólo implica que el paciente esté libre de síntomas depresivos o estos sean mínimos, sino también implicaría un restablecimiento de la funcionalidad previa al episodio (Keller, 2003). Sin embargo, los aspectos funcionales en la remisión del episodio depresivo mayor han sido estudiados generalmente de una forma secundaria, quedando aspectos sin resolver.

Específicamente, si bien se sabe que la remisión parcial con presencia de síntomas residuales, se asocia a una alteración del funcionamiento global, laboral social, etc. (Miller *et al.,* 1998; Simon *et al.,* 2000; Trivedi *et al.,* 2009), no se conoce bien cuál es el impacto de esta remisión parcial del episodio depresivo sobre el pronóstico funcional del paciente. Cabe reseñar que los pocos estudios que evalúan los aspectos funcionales asociados a la remisión proceden de análisis secundarios de ensayos clínicos randomizados (Miller *et al.,* 1998; Simon *et al.,* 2000; Trivedi *et al.,* 2009) siendo escasa la evidencia procedente de muestras más representativas de la práctica clínica habitual.

Asimismo, no se ha estudiado cual es la contribución de los distintos síntomas residuales (nucleares, ansiosos, de insomnio, etc.) sobre la alteración de la

funcionalidad. Los pocos estudios que han evaluado el impacto de los síntomas residuales sobre la funcionalidad del paciente (Miller *et al.,* 1998; Zimmerman *et al.,* 2007) lo han hecho de una forma global, es decir, no hay estudios evaluando el papel específico de cada tipo de síntoma residual.

Tampoco, se conoce en qué medida la remisión clínica, definida por una puntuación ≤7 en la escala de Hamilton para la depresión (HAMD-17), predice una funcionalidad normal. Es decir, existe controversia sobre qué punto de corte de la HAMD-17 refleja mejor, no solo la ausencia de síntomas, sino también la ausencia de alteración funcional. Es posible que esta controversia se derive de la escasez de estudios al respecto.

La evaluación actual de la remisión es unidimensional ya que se basa en una puntuación en una escala sintomática sin tener en cuenta otros aspectos como los aspectos funcionales o de calidad de vida considerados importantes por los pacientes. Se desconoce cuál es la implicación pronóstica de definir la remisión de una forma más amplia, teniendo en cuenta no sólamente factores sintomáticos, sino también aspectos funcionales, de calidad de vida y de salud mental positiva.

II-HIPÓTESIS DE TRABAJO y OBJETIVOS

II- HIPOTESIS DE TRABAJO Y OBJETIVOS

A tenor de lo expuesto, la presente tesis se enmarca dentro del objetivo general de contribuir a un mejor conocimiento de la relación existente entre la remisión clínica y la funcionalidad en el trastorno depresivo mayor.

Específicamente se pretende confirmar las siguientes hipótesis:

1. La remisión parcial del episodio tras el tratamiento agudo se asocia a una peor evolución funcional del paciente en comparación con la remisión completa.
2. El punto de corte en la escala de Hamilton para la depresión que mejor predice una funcionalidad normal podría ser menor al punto de corte que define remisión (HAMD-17 ≤7)
3. El peso que tienen distintos síntomas residuales (nucleares, ansiosos, de insomnio, etc) sobre la alteración de la funcionalidad es diferente.

Para ello se han generado unos objetivos específicos:

OBJETIVO 1

Estudiar cual es el impacto de la presencia de síntomas residuales (remisión parcial) tras el tratamiento agudo en el pronóstico funcional del paciente con depresión.

Diseño:

Estudio epidemiológico, multicéntrico, prospectivo de 6 meses de seguimiento con dos cohortes de pacientes emparejadas por sexo, edad y centro. Cohorte 1: pacientes que tras tres meses de tratamiento agudo presentan una remisión completa del episodio de depresión (HAMD-17 ≤7, N=146). Cohorte 2: pacientes que tras tres meses de

tratamiento agudo presentan una remisión parcial (HAMD-17 >7 y ≤15, N= 146) tras. Este estudio se presenta como el Estudio I de la actual tesis.

OBJETIVO 2

Evaluar cuál es el punto de corte en la escala de Hamilton para la depresión que mejor predice una funcionalidad normal.

Diseño:

Análisis post-hoc de sensibilidad y especificidad basados en Curvas ROC (Receiver Operating Characteristics) realizado sobre el Estudio I. El análisis incluyó a los 292 pacientes de dicho estudio [pacientes (n=146) en remisión completa (HAMD-17 ≤7) y pacientes (n= 146) en remisión parcial (HAMD-17 >7 y ≤15)] y se realizó al final del los 6 meses de seguimiento.

OBJETIVO 3

Evaluar el peso de distintos tipos de síntomas residuales sobre la alteración de la funcionalidad en el paciente con depresión.

Diseño:

Análisis post-hoc realizado sobre un estudio epidemiológico, observacional prospectivo de un año de seguimiento que incluyó a 930 pacientes con diagnóstico de episodio de depresión mayor (Estudio II; Ciudad *et al*., 2012). El análisis incluyó a los pacientes que fueron respondedores (reducción en la puntuación total del HAMD-17 ≥ al 50% desde el momento basal) tras tres meses de tratamiento agudo (N=624).

En la figura 1 se resume los objetivos específicos de la tesis, el diseño de los Estudios I y II, así como las publicaciones que se presentan como parte de la actual tesis.

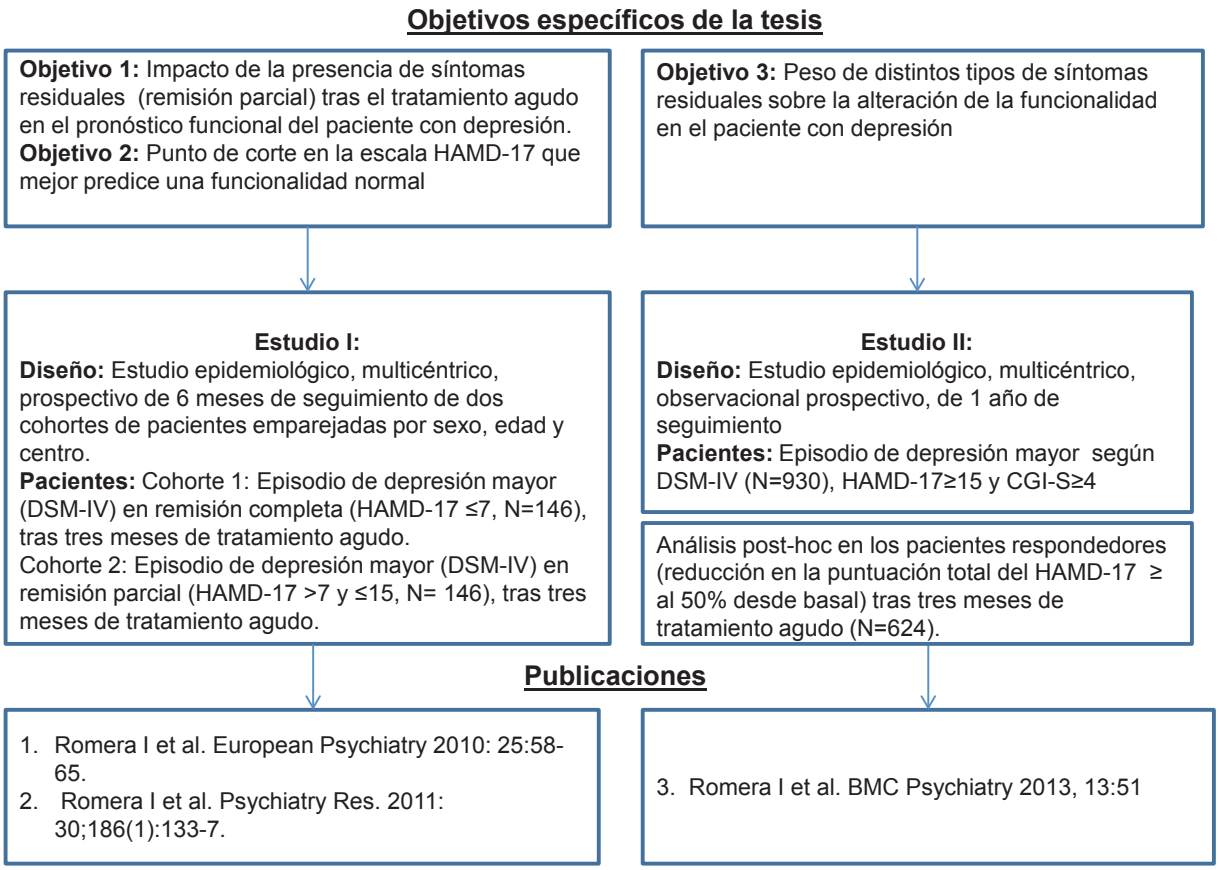


Figura 1: Objetivos específicos de la tesis, diseño de los Estudios I y II y publicaciones

III-MÉTODO

III- MÉTODO

El método se describe de forma detallada en cada uno de los artículos originales. En este apartado se exponen los aspectos esenciales de las poblaciones de estudio, diseño, evaluación de resultados y estadística. El protocolo del Estudio I fue aprobado por el comité ético del Hospital of Bellvitge. El protocolo del Estudio II fue aprobado por el comité ético del Hospital Puerta de Hierro de Madrid.

ESTUDIO I

Se trata de un estudio epidemiológico, multicéntrico, prospectivo de 6 meses de seguimiento con dos cohortes de pacientes emparejadas por sexo, edad y centro.

PACIENTES

Se incluyeron pacientes ambulatorios con una edad de al menos 18 años, diagnosticados de trastorno depresivo mayor sin rasgos psicóticos según criterios del DSM-IV y con al menos un episodio depresivo previo. En el momento de la inclusión los pacientes debían estar en remisión completa (HAMD-17 ≤7) o parcial (HAMD-17 = 8-15) del episodio depresivo. Todos los pacientes recibieron tratamiento antidepresivo para el episodio depresivo actual durante los tres meses previos a su inclusión.

Se excluyeron aquellos pacientes que presentaban diagnóstico previo de trastorno bipolar, esquizofrenia u otro trastorno psicótico; trastorno distímico o trastorno adaptativo actual; una puntuación total en la HAMD-17 >15.

Todos los pacientes firmaron el consentimiento informado antes de su participación en los estudios.

DEFINICIONES Y EVALUACIÓN DE RESULTADOS

Se consideró remisión parcial del episodio cuando no existían criterios DSM-IV para el episodio depresivo y la puntuación en el HAMD-17 era mayor de 7 y menor o igual a 15.

Se considero remisión completa del episodio cuando no existían criterios DSM-IV para el episodio depresivo y la puntuación en el HAMD-17 era menor o igual a 7.

La variable de resultado principal fue la funcionalidad global al final del periodo de seguimiento, evaluado mediante la escala SOFAS (Social and Occupational Functioning Assessment Scale) (Goldman,1992). También se evaluó la funcionalidad laboral mediante la presencia y número de días de baja laboral. La severidad de la depresión se valoró mediante la escala de HAMD-17 y la CGI-S.

La escala SOFAS valora globalmente el nivel de funcionalidad social y ocupacional en un continuo que va desde un estado de funcionalidad óptima a un estado de importante alteración funcional. De forma que 100 representa hipotéticamente la situación más sana y 1 la mayor alteración funcional posible. Se valora únicamente el nivel funcional sin tener en cuenta los síntomas y es completada por el clínico. Los intervalos más altos de la SOFAS, 81-90 y 91-100, describen a individuos sin psicopatología significativa y que presentan muchos rasgos de salud mental positiva, un amplio rango de intereses, efectividad social, etc. Por lo que una puntuación ≥ 80 en la SOFAS se considera un nivel normal de funcionamiento (APA 2005).

Finalmente, la recaída se definió como un incremento de al menos dos puntos en la CGI-S con respecto a la visita basal y cumplir criterios de episodio depresivo mayor según DSM-IV al final de estudio

ANÁLISIS ESTADÍSTICO

El tamaño muestral del Estudio I se calculó para detectar una diferencia al menos de 5 en la escala SOFAS entre el grupo de pacientes en remisión parcial y el grupo de

pacientes en remisión completa, con un nivel de significación del 5% y un poder estadístico del 80%, en un contraste bilateral con muestras pareadas. Una muestra de 300 pacientes (150 por cohorte) se consideró apropiada, asumiendo una desviación estándar de la diferencia de 20 y una tasa de abandonos del 20%.

Para estudiar el impacto de la presencia de síntomas residuales (remisión parcial) tras el tratamiento agudo sobre el pronóstico funcional de los pacientes con depresión, se analizaron las diferencias en el funcionamiento (puntuación total de la SOFAS), entre ambos grupos (remisión parcial vs. remisión completa) en el momento basal, tras 3 y 6 meses de seguimiento, mediante el test estadistico-t para muestras emparejadas. Las comparaciones porcentuales sobre el funcionamiento se realizaron mediante el test de McNemar. Se comparó entre ambas cohortes el porcentaje de pacientes en baja laboral durante los 6 meses del estudio (McNemar test) y el número medio de días de baja laboral (test estadístico-t para muestras emparejadas). Para valorar los factores asociados a un nivel funcional normal (SOFAS ≥ 80), al final del estudio se realizó un modelo de regresión logística siendo el estado funcional a los 6 meses la variable dependiente.

Para evaluar cuál es el punto de corte en la escala de Hamilton de depresión que mejor predice una funcionalidad normal (SOFAS total ≥ 80), se realizaron análisis de sensibilidad y especificidad basados en Curvas ROC (Receiver Operating Characteristics) a los seis meses de seguimiento sobre el Estudio I. Se calcularon la especificidad, sensibilidad y valores predictivos positivos y negativos así como el área bajo la curva y su intervalo de confianza. Se calcularon otras dos curvas ROC para un nivel normal de funcionalidad (SOFAS total ≥ 80) a los seis meses usando la sub-escala HAM-D6 (ítems de ánimo deprimido, culpa, trabajo, retardo, ansiedad psíquica y síntomas somáticos de la HAMD-17; Bech *et al.,* 1981) y el ítem 1 (ánimo deprimido) de la HAMD-17. También se evaluó la correlación entre la funcionalidad social y

ocupacional (SOFAS) y la gravedad de la depresión (HAMD-17) basalmente, a los tres meses y al final del estudio a los 6 meses mediante el coeficiente de Pearson.

ESTUDIO II

Se trata de un estudio epidemiológico, observacional prospectivo de un año de seguimiento que incluyó a una cohorte de 930 pacientes con diagnóstico de episodio de depresión mayor (Ciudad *et al.,* 2012). Sobre este estudio epidemiológico, como parte de esta tesis, se ha realizado un análisis post-hoc que incluyó a la cohorte de pacientes que fueron respondedores (reducción en la puntuación total del HAMD-17 ≥ al 50% desde el momento basal), tras tres meses de tratamiento agudo (N=624).

PACIENTES

Se incluyeron pacientes ambulatorios de al menos 18 años de edad, diagnosticados de episodio actual de trastorno depresivo mayor sin rasgos psicóticos, según criterios del DSM-IV, con una puntuación total ≥15 en la HAMD-17 y una puntuación ≥ 4 en el CGI-S. Para episodios recurrentes, se precisó que el paciente hubiese estado un periodo de al menos 12 semanas en remisión entre el episodio actual y el previo. Aquellos pacientes que estuviesen en tratamiento antidepresivo y hubiese cambiado en las doce semanas previas al comienzo del episodio actual fueron excluidos. También se excluyeron pacientes que presentaran otro diagnóstico del Axis 1, demencia o alteración cognitiva.

Todos los pacientes firmaron el consentimiento informado antes de su participación en los estudios.

DEFINICIONES Y EVALUACIÓN DE RESULTADOS

Para la realización del análisis post-hoc se definió al paciente respondedor cuando hubo reducción en la puntuación total del HAMD-17 ≥ al 50% tras tres meses de tratamiento agudo (N=624).

La variable de resultado principal fue la funcionalidad global a los tres meses de seguimiento, evaluado mediante la escala SOFAS (Social and Occupational Functioning Assessment Scale) (Goldman, 1992).

A los tres meses de tratamiento agudo, en esta población de respondedores, se evaluó la severidad de la depresión mediante la escala de HAMD-17. Así mismo, se evaluaron específicamente los síntomas residuales nucleares (sub-escala nuclear de la HAMD-17 ≥ 1), de insomnio (sub-escala sueño de la HAMD-17 ≥1), ansiosos (sub-escala ansiedad de la HAMD-17 ≥1) y somáticos (ítem 13 de la HAM-D17- ≥1) así como el dolor (escala analógica visual-dolor ≥30). Para definir los distintos tipos de síntomas residuales (nucleares, ansiosos, de insomnio, etc) nos basamos en la definición utilizada previamente por Dombrovsky y colaboradores, 2008. La sub-escala nuclear incluye los items de ánimo deprimido (Item 1), culpa (Item 2), suicidio (Item 3), y anergia/anhedonia (Item 7) de la HAMD-17. La sub-escala de sueño incluye los ítems de insomnio de la HAM-D17 (Item 4, Item 5, Item 6). La sub-escala de ansiedad incluye los ítems de agitation (Item 9), ansiedad psíquica (Item 10), ansiedad somática (Item 11) e hipocondriasis (Item 15).

ANÁLISIS ESTADÍSTICO

Para evaluar la asociación entre los dominios de síntomas residuales y el funcionamiento del paciente se ha desarrollado un modelo de regresión logística siendo la variable dependiente un nivel normal de funcionamiento después de 3 meses

de tratamiento (puntuación total SOFÁS ≥ 80), y los siguientes factores como las variables independientes: La edad como variable continua, sexo, estado civil, situación laboral, nivel educativo, el funcionamiento basal (puntuación SOFÁS), la gravedad inicial de la depresión (HAMD-17), la presencia de episodios previos de depresión, co-morbilidades médicas, duración del episodio actual, los síntomas residuales a los 3 meses (síntomas nucleares, síntomas de insomnio, síntomas de ansiedad, síntomas somáticos), y el dolor a los 3 meses. Todas las variables independientes se incluyeron en el modelo inicial y luego se excluyeron paso a paso las no significativas (umbral para el valor p = 0,05). Se testaron las interacciones entre las variables (razón de probabilidad). Los pacientes con información sobre las variables se incluyeron en el modelo (n = 600). El modelo reducido se presentó en términos de odds ratio (OR) y sus intervalos de confianza del 95% (IC).

Para determinar y comparar la sensibilidad y especificidad de los dominios de síntomas residuales y del dolor, como indicadores de niveles normales de funcionamiento (puntuación SOFÁS ≥ 80) a 3 meses de tratamiento, se calcularon curvas ROC (Receiver operating characteristics curves).

IV- RESULTADOS

- **TRABAJO 1:** Romera I, Perez V, Menchón J.M, Delgado-Cohen H, Polavieja P, Gilaberte I. Social and occupational functioning impairment in patients in partial versus complete remission of a major depressive disorder episode. A six-month prospective epidemiological study. European Psychiatry 2010: 25:58-65.

- **TRABAJO 2:** Romera I, Pérez V, Menchón JM, Polavieja P, Gilaberte I. Optimal cutoff point of the Hamilton Rating Scale for Depression according to normal levels of social and occupational functioning. Psychiatry Res. 2011: 30; 186(1):133-7.

- **TRABAJO 3:** Romera I, Pérez V, Ciudad A, Caballero L, Roca M, Polavieja P, Gilaberte I. Residual symptoms and functioning in depression, does the type of residual symptom matter? A post-hoc analysis. BMC Psychiatry 2013, 13:51

Available online at ScienceDirect
www.sciencedirect.com
Elsevier Masson France
EM|consulte
www.em-consulte.com
EUROPEAN PSYCHIATRY
European Psychiatry 25 (2010) 58–65

Original article

Social and occupational functioning impairment in patients in partial versus complete remission of a major depressive disorder episode. A six-month prospective epidemiological study

I. Romera [a,*], V. Perez [b], J.M. Menchón [c], H. Delgado-Cohen [a], P. Polavieja [a], I. Gilaberte [a]

[a] *Clinical Research Department, Lilly, SA, Avenida de la Industria, 30, Alcobendas, 28108 Madrid, Spain*
[b] *Department of Psychiatry, Hospital de Sant Pau i de la Santa Creu, C/Sant Antoni Maria Claret, CIBERSAM, 167, 08025 Barcelona, Spain*
[c] *Department of Psychiatry, Hospital Universitari de Bellvitge, Feixa Llarga sn, Hospitalet de Llobregat, CIBERSAM, 08907 Barcelona, Spain*

Received 6 October 2008; received in revised form 30 December 2008; accepted 19 February 2009
Available online 23 June 2009

Abstract

Purpose: To evaluate social and occupational functioning in patients in partial remission (PR) compared with patients in complete remission (CR) of a major depressive disorder (MDD) episode.
Subjects and methods: This is a six-month prospective study. PR was defined as a score more than 7 and less or equal to 15 in the Hamilton Depression Rating Scale, and CR as less or equal to 7. All patients had been on acute antidepressant treatment during the previous three months and no longer met criteria for MDD. Functioning was assessed by the Social and Occupational Functioning Assessment Scale (SOFAS).
Results: Mean (S.D.) patient age was 50.5 (14.5) years ($N = 292$) and 77% were female. At baseline, partial remitters showed greater impairment in social and occupational functioning than complete remitters (62.8 [12.6] versus 80.4 [10.5], respectively; $P < .0001$). After six months, only 47% PR versus 77% CR reached normal functioning, and SOFAS ratings for PR were below normal range (76.2 [12.3] PR versus 84.6 [9.4] CR; $P < .0001$). PR reported three times more days absent from work due to sickness than CR (63 days versus 20 days; $P < .001$).
Conclusion: We conclude that PR of an MDD episode is associated with significant functional impairment that persists even after nine months of antidepressant treatment. Our results underline the importance of treating the patient until achieving full remission.

Keywords: Major depressive disorder; Social and occupational functioning; Partial remission

1. Introduction

The optimal goal in treatment of patients with major depressive disorder (MDD) should be the resolution of both symptoms and functional impairment [5,15]. However, approximately one third of patients fails to achieve full remission and suffers from residual symptoms [13,23].This is known as partial remission (PR), and it is characterized by the presence of symptoms such as depressed mood, anxiety, somatic symptoms and sexual dysfunction, without meeting criteria for MDD [20,23]. The persistence of PR has been associated with an increased risk of relapse [23], shorter time to relapse [13], poorer quality of life [2,4] and disability [4].

There are few studies that have evaluated the psychosocial and functional outcomes of depression and they all have pointed to a poor outcome [16]. Social and occupational impairments have also been observed in patients with depression compared with other chronic medical conditions [1,11,29]. In these studies patients with depression showed comparable, if no greater, levels of social and occupational impairments than those with other chronic medical disorders. Moreover, the significant impairments that depressed patients have in numerous areas of social and interpersonal functioning lead to high levels of unemployment, disability and decreased work performance [1,3,19]. These impairments have serious effects on the patients, their families and, ultimately, the community. In fact, depression is the most prevalent mental disorder causing absence from work due to sickness [29], and the increasing number of disability pensions granted for major depression is a major concern [26].

* Corresponding author. Tel.: +34 91 663 50 00; fax: +34 91 663 52 31.
E-mail address: romera_irene@lilly.com (I. Romera).

0924-9338/$ – see front matter © 2009 Elsevier Masson SAS. All rights reserved.
doi:10.1016/j.eurpsy.2009.02.007

The presence of residual symptoms after the completion of acute antidepressant treatment has been found to be associated with higher functional impairment in chronically depressed patients [18]. Previous research suggests that antidepressant treatment may improve psychosocial impairments found in chronic depression and that residual symptoms are more common in more severe initial illness [18,23].

Therefore, depressive disorders include both depressive symptoms and functional impairments that should be effectively addressed in order to improve prognosis and treatment for these patients. There are few studies that have evaluated PR in major depression, or their consequences [2,4,13,14,18,21]. However, they have focused mainly on the symptomatic aspects (description of residual symptoms, risk of relapse or recurrence, etc.), but little emphasis has been made on social and occupational functioning, which is also of importance both to patients and to their families. There is still limited information on the impact of PR of an MDD episode on the functional prognosis of depression during ongoing treatment. Here we sought to evaluate functional impairment in patients who, after three months of acute antidepressant treatment, were in PR versus those who were in complete remission (CR) of an MDD episode over a six-month period. Therefore, we hypothesized that not achieving CR after completion of acute pharmacological treatment of a depressive episode would be associated with a poor outcome in the functional evolution of the depressive episode. In addition, we assessed the differences among patients in PR and those in CR in terms of depressive symptoms improvement, relationship between depressive symptomatology and social and occupational functioning, relapse and remission rates and sick leave.

2. Subjects and methods

2.1. Study design

This was a six-month, multicenter, prospective epidemiological study. Two cohorts of patients were investigated: a cohort of patients in PR and a cohort of patients in CR, in 36 psychiatric consultation centers throughout Spain.

Patients were consecutively recruited and were pair-wise matched by age, gender and health-care area. The matching of patients was the investigator's responsibility. Inclusion of the same number of partial and complete remitters in each age and gender stratum was required. A consecutive recruitment of patients in PR per site was carried out, followed by a consecutive recruitment of patients in CR, matched for age and gender with each partial remitter previously recruited.

Treatment pattern and treatment initiation or changes for MDD were solely at the discretion of the physician and the patient, and according to usual standard of care. Patients were enrolled in this study solely for the collection of data on the observations made during normal clinical practice. No interventions outside usual clinical practice were performed.

2.2. Study population, selection criteria and definitions

Patients were eligible for the study if they were outpatients of more than or equal to 18 years and had at least one episode of MDD prior to the one at study entry. Patients in PR of the episode had to have had an episode of MDD without psychotic features, as defined by the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV), diagnosed by the investigator, and who after 12 weeks (± 2 weeks) of acute antidepressant treatment were in PR of the episode. Patients in CR of the episode had to have had an episode of MDD without psychotic features, as defined by DSM-IV, diagnosed by the investigator, and who after 12 weeks (± 2 weeks) of acute antidepressant treatment were in CR of the episode. Patients were excluded if they had:

- a previous diagnosis of bipolar disorder, schizophrenia or other psychotic disorder;
- a current diagnosis of dysthymic disorder or adjustment disorder;
- a 17-item Hamilton Depression Rating Scale (HAMD-17) total score greater than 15.

At the time of inclusion, patients were in PR or CR and were previously treated for 12 weeks (± 2 weeks). The diagnosis of the MDD episode was made by the investigator, who also was the treating psychiatrist. Patients were required to have a history of at least one previous depression episode.

Patients were considered to be in CR if they did not meet criteria for MDD, as defined by the DSM-IV, and had a HAMD-17 total score less than or equal to 7. Patients were considered to be in PR if they did not meet criteria for MDD, as defined by DSM-IV, and had a HAMD-17 total score greater than 7 and equal to or less than 15.

The local ethical review board of the Hospital of Bellvitge provided approval of the study protocol in accordance with the principles of the Declaration of Helsinki. All patients provided written informed consent after the study was explained and prior to the collection of data.

2.3. Study assessments

We examined social and occupational functioning and depression severity at baseline (at this point patients had been on acute antidepressant treatment for approximately three months) and after approximately 12 and 24 weeks (i.e., three and six months). Sociodemographic and clinical data were collected at baseline. Social and occupational functioning was assessed by the Social and Occupational Functioning Assessment Scale (SOFAS) [7] and severity of the MDD episode was assessed by the HAMD-17 [9,10]. At all observations functioning, depression severity and antidepressant therapy were evaluated. In addition, sick leave data and self-reported disability, for unemployed patients, were collected at baseline and at the end of the study.

The SOFAS [7] is a 100-point single-item scale used to indicate the individual's level of social and occupational

functioning across a continuum ranging from a state of optimum functioning to a state of important functional impairment. It measures purely the level of social and occupational functioning, without taking symptoms into account. Thus, a value of 1 represents the hypothetically most impaired individual and 100 represents the hypothetically healthiest individual. It is completed by a clinician, using information from any clinical source (e.g., clinical evaluation of the patient, case record, etc.). The scale includes impaired function due both to physical limitations and to mental problems. The two highest intervals on the SOFAS, 81–90 and 91–100, describe individuals who not only are without significant psychopathology, but who also exhibit many traits often referred to as components of positive mental health, such as superior functioning, a wide range of interests, social effectiveness, warmth and integrity. Although some individuals rated above 70 may seek some form of assistance for psychological problems, the vast majority of individuals in treatment are rated between 1 and 70. Most outpatients are rated between 31 and 70, and most inpatients are rated between 1 and 40 [28]. Considering the above information, a SOFAS score more than or equal to 80 was used in this study to define normal levels of functionality.

Relapse was defined as having an increase in Clinical Global Impression-Severity (CGI-S) score of at least two points in relation to baseline and meeting criteria for MDD at final observation. The CGI-S is a single-item rating of the clinician's assessment of the severity of the patient's symptoms. The severity score ranges from 1 (normal, not at all ill) to 7 (among the most extremely ill patients) [8].

Finally, data regarding whether the dose of antidepressant was below, above or within the recommended range based on the antidepressant label, was collected for each patient and at all observations. However, no data regarding each antidepressant precise dosing were gathered.

2.4. Indirect cost estimation

The costs associated to a specific disease are usually divided into direct, indirect and intangible costs. Indirect costs are the value of production lost to society due to absence from work, disability and death. In our study, we focused on estimating indirect cost of short-term sick leave over a six-month period based on the working population only. For this purpose, we recorded data on the working status and the number of days on short-term sick leave retrospectively for the whole study period (six months). At baseline the number of days on sick leave was recorded only for the last three months.

For the estimation of indirect costs and the subsequent conversion into monetary units, the human capital approach was used [12]. According to this, indirect costs are estimated as the gross income lost during the time of absence from work. The calculation is based on per capita average wages for the third quarter of 2007 obtained from the National Quarterly Labour Cost Survey (INE [National Statistics Institute], 2007. National Quarterly Labour Cost Survey. Accessed online 10th March 2007 at http://www.ine.es/welcoing.htm).

2.5. Statistical Analysis

Sample size was calculated to detect a minimal difference of 5.16 in the SOFAS scale between partial and complete remitters, considered clinically relevant [13], with a level of significance of 5% and a statistical power of 80%, in a bilateral contrast with paired samples. A sample of 300 patients was considered to be appropriate (150 patients in each cohort), assuming a standard deviation (S.D.) of the difference of 20 and a withdrawal rate of 20%.

Patient continuous variables were described using means and S.D., or by absolute and relative frequencies. Baseline comparisons were made through a paired *t*-test for continuous variables and a McNemar test for qualitative variables. A paired *t*-test was used to analyze the differences in functioning between the two cohorts as assessed by the SOFAS scale total score. Functioning comparisons at baseline and at three and six months were performed by McNemar test, and depression severity comparisons by paired *t*-test. Pearson correlation coefficients between social and occupational functioning (SOFAS) and depression severity (HAMD-17) total scores at baseline were computed in order to assess the association between the two scales.

Percentage comparisons between cohorts of patients on sick leave (only working population) at any time during the previous six months (McNemar test), and the mean number of days of sick leave were performed by means of *t*-statistic test for paired samples.

In order to assess factors associated with achieving normal functioning at six months (SOFAS $\geq$80), a logistic regression model was performed including the functioning status (normal versus not) at six months of follow-up as the dependent variable, and baseline sociodemographic and clinical patients' characteristics as independent variables. This model included exclusively data from patients with a baseline SOFAS score below 80.

3. Results

3.1. Patient characteristics

This study was performed between April 2006 and May 2007. A total of 292 patients (146 in each cohort) entered the study. At three months, one patient dropped out due to one missing observation. Consequently, the pair from the other cohort was eliminated from the analysis, leaving 290 patients, 145 in each cohort. At six months, a total of two patients were lost to follow-up and two dropped out, leaving 286 eligible patients, 143 in each cohort.

Table 1 summarizes patients' clinical and demographic characteristics. The sample was predominantly female (77.4%) with a mean age of 50.5 years. When comparing both groups at baseline, we found significant differences in the following characteristics: a total of 23.9% of complete remitters had university level studies compared with 10.9% of partial remitters (McNemar, $P < .05$), and significantly more partial remitters reported a history of personality and dysthymic disorders than complete remitters. Patients in the PR group had,

Table 1
Baseline sociodemographic and clinical characteristics of patients in partial remission (PR) versus patients in complete remission (CR) of an major depressive disorder (MDD) episode.

	Total $N = 292$	Complete remission $N = 146$	Partial remission $N = 146$
Age (years), mean (S.D.)	50.5 (14.5)	50.3 (15.0)	50.7 (14.1)
Female, *N* (%)		113 (77.4)	113 (77.4)
Male, *N* (%)		33 (22.6)	33 (22.6)
Education (%)			
No education	7.5	8.9	6.2
Primary level education	42.5	37.7	47.3
Secondary level education	32.5	29.4	35.6
University level education*	17.5	23.9	10.9
Work			
Not paid (%)	50.7	47.3	54.1
Self-reported disability in the last month (%)*	48.6	36.2	59.5
Days of self-reported disability, mean (S.D.)**	8.5 (1.1)	3.9 (7.4)	12.5 (12.3)
Paid (%)	49.3	52.7	45.9
Absent in the last 3 months (%)**	65.9	54.5	79.1
Days of absence, mean (S.D.)**	31.9 (33.3)	21.4 (27.2)	44.0 (35.7)
MDD episodes			
Age of onset of first MDD episode, years, mean (S.D.)	37.8 (14.0)	37.3 (13.6)	38.4 (14.5)
Number of previous depression episodes, mean (S.D.)	3.6 (3.8)	3.8 (4.4)	3.5 (3.2)
Total duration of the current episode, weeks, mean (S.D.)	19.5 (11.5)	18.8 (9.9)	20.1 (12.8)
History of psychiatric disorders (%)			
At least one*	30.8	25.3	36.3
Personality disorder*	5.5	2.0	8.9
Dysthymic disorder*	8.6	5.5	11.6
Adaptative disorder	15.7	13.7	17.8
Anxiety disorder	12.7	9.6	15.7
Antidepressant treatment (%)			
SNRI	42.8	41.8	43.8
SSRI	37.7	39.1	36.3
NaSSA	4.4	3.4	5.5
Combination	13.0	12.3	13.7
Other	2.1	3.4	0.7
Depression severity			
HAMD-17 mean total score (S.D.)**	8.2 (4.3)	4.3 (1.8)	12.1 (2.1)

*$P < .05$; **$P < .001$: paired *t*-test for means and McNemar test for percentages; S.D.: standard deviation; MDD: major depressive disorder; SNRI: serotonin and norepinephrine reuptake inhibitors; SSRI: selective serotonin reuptake inhibitors; NaSSA: Noradrenergic and Specific Serotonergic Antidepressant; HAMD-17: 17-item Hamilton Depression Rating Scale.

by definition, significantly higher score in HAMD-17 than patients in the CR group (mean [S.D.] = 12.0 [2.1] and 4.3 [1.8], respectively; paired *t*-test, $P < .001$).

At baseline, a significantly higher percentage of employed partial remitters had been on sick leave (79.1% and 54.5%, respectively; McNemar, $P = .003$) and had been absent from work more days in the previous three months than employed complete remitters (mean [S.D.] = 44 [35.7] days versus 21.4 [27.2] days; paired *t*-test, $P < .001$). On the other hand, more patients in the PR group reported performing unpaid work, with significantly higher rates of self-reported disability (59.5% versus 36.2%, McNemar, $P < .008$), and more days of self-reported disability in the previous month than complete remitters (mean [S.D.] 12.5 [12.3] days versus 3.9 [7.4] days, paired *t*-test, $P < .001$) (Table 1).

The two groups did not differ in any other clinical variable at baseline, including age at onset of first MDD episode, number of previous depression episodes, total duration of the current episode, history of adaptative or anxiety disorder, and type of antidepressant treatment. At baseline, all patients had been in acute antidepressant treatment for three months. In this regard, a high percentage of patients were administered serotonin and norepinephrine reuptake inhibitors (SNRI) (42.8%) or selective serotonin reuptake inhibitors (SSRI) (37.7%), and to a lesser extent Noradrenergic and Specific Serotonergic Antidepressant (NaSSA) (4.4%), a combination of antidepressants (13%) or other (2.1%).

3.2. Social and occupational functioning

At baseline, the CR group showed significantly higher SOFAS mean score than the PR group (mean [S.D.] = 80.4 [10.5], 95%CI = 78.7, 82.1 and 62.8 [12.6], 95%CI = 60.8, 64.9 respectively, paired *t*-test, $P < .0001$), and the majority of

Table 2
SOFAS and HAMD-17 mean scores at baseline, three and six months.

	SOFAS mean score (S.D.)		HAMD-17 mean score (S.D.)	
	Complete remission	Partial remission	Complete remission	Partial remission
Baseline (No. pairs: 146)	80.4 (10.5)*	62.8 (12.6)	4.3 (1.8)**	12.0 (2.1)
Month 3 (No. pairs: 145)	82.6 (11.3)*	71.8 (13.3)	4.5 (3.9)**	8.3 (4.3)
Month 6 (No. pairs: 143)	84.6 (9.4)*	76.2 (12.3)	4.0 (3.5)**	7.2 (4.6)

*$P < .0001$ (paired t-test) versus partial remission; **$P < .001$ (paired t-test) versus partial remission; S.D.: standard deviation; SOFAS: Social and Occupational Functioning Assessment Scale; HAMD-17: 17-item Hamilton Depression Rating Scale.

complete remitters already showed normal functioning (SOFAS $\geq$80) unlike partial remitters (Table 2). While both groups showed a higher SOFAS score at three months, complete remitters had a significantly higher SOFAS mean score than partial remitters (mean [S.D.] 82.6 [11.3], 95%CI = 80.8, 84.5 and 71.8 [13.3], 95%CI = 69.6, 73.9, paired t-test, $P < .0001$). This difference remained statistically significant at six months (mean [S.D.] 84.6 [9.4], 95%CI = 83.0, 86.1 and 76.2 [12.3], 95%CI = 74.15, 78.2, paired t-test, $P < .0001$). At endpoint, the PR group had not achieved normal functioning as evidenced by a SOFAS mean score less than 80 (Table 2).

Fig. 1 shows the percentage of patients in both groups showing normal functional levels at all time points. At baseline, 67% of complete remitters and 8% of partial remitters (McNemar test, $P < .001$) had a SOFAS mean score more than or equal to 80. Significantly more complete remitters achieved normal functioning than partial remitters at three months (74% and 31% respectively, McNemar test, $P < .001$). Moreover, at endpoint only 47% of partial remitters achieved normal functioning compared with 77% of complete remitters, despite both groups of patients being on antidepressant treatment for six months of study period plus three months of previous acute antidepressant treatment (McNemar test, $P < .001$).

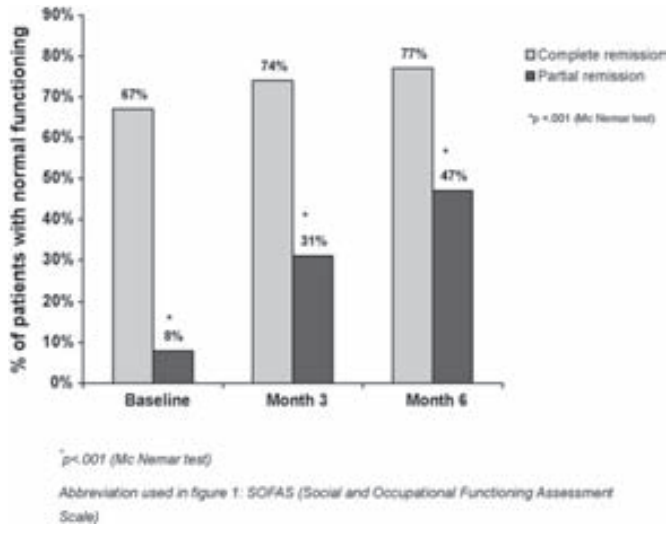


Fig. 1. Percentage of patients who reached normal functional level (SOFAS $\geq$80) at baseline, three and six months. SOFAS: Social and Occupational Functioning Assessment Scale.
*$P < .001$ (McNemar test).

3.3. Depression severity

Patients in CR showed significantly lower HAMD-17 mean scores at all time points than patients in PR, whom by definition had higher scores than those who had remitted completely (Table 2). The individual mean change in the HAMD-17 score from baseline to endpoint was significantly greater in partial remitters than complete remitters (-4.83 versus -0.31, respectively; t-test for paired samples, $P < 0.001$).

The percentage of partial remitters who achieved CR (HAMD-17: $\leq$7) at month three and at the end of the study was 40 and 59% respectively, whereas 85 and 84% of complete remitters maintained remission at three and six months, respectively (McNemar, $P < .001$). No significant differences were found between groups in the percentage of patients having a relapse throughout the study (8.2% of partial remitters versus 7.5% of complete remitters; McNemar, $P = 1.0$).

3.4. Relationship between depression severity and social functioning

We found that there was a high correlation between the SOFAS and HAMD-17 scales throughout the study (Pearson correlations: at baseline -0.62, $P < .0001$; at endpoint -0.63, $P < .0001$), meaning that improvements in symptom severity and functional impairment from depression are significantly correlated.

3.5. Factors associated with achieving normal functioning (SOFAS $\geq$80) at endpoint

The results from the logistic regression analysis on the subsample of patients with a baseline SOFAS score below 80 and who completed the study ($N = 179$, CR = 47 and PR = 132) showed that the most significant factor associated with achieving normal functioning at endpoint was being in CR at baseline (Fig. 2). The odds of achieving normal functioning at six months were three times higher in those patients who at baseline were in CR (OR = 3.2; 95%CI = 1.3, 7.6) and 1.3 times higher in those who showed a reduction on the HAMD-17 (OR = 1.3; 95%CI = 1.2, 1.5; for two points score reduction) throughout the study. Non-significant associations were found for number of previous depression episodes, history of personality or dysthymic disorder and for antidepressant switch throughout the study.

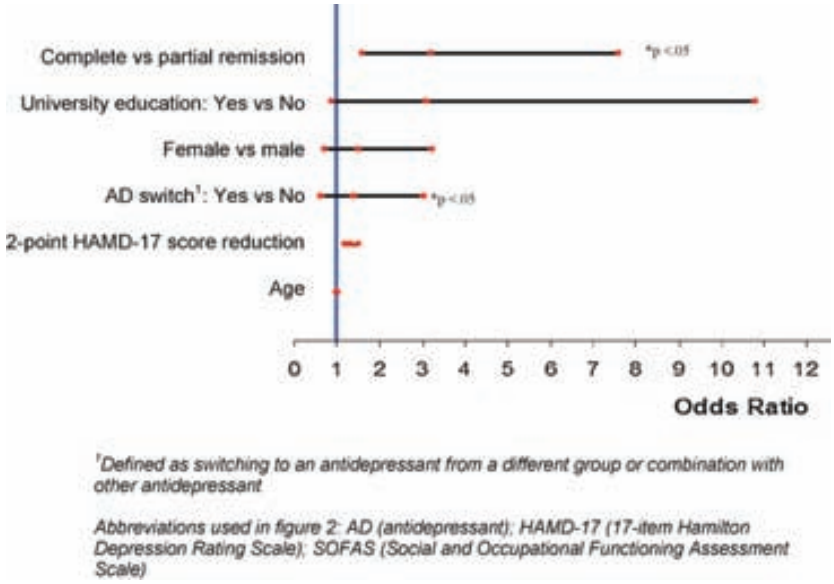


Fig. 2. Factors associated with reaching normal functional levels (SOFAS ≥80) at six months. AD: antidepressant; HAMD-17: 17-item Hamilton Depression Rating Scale; SOFAS: Social and Occupational Functioning Assessment Scale.
[1]Defined as switching to an antidepressant from a different group or combination with other antidepressant.

3.6. Sick leave and indirect cost estimation

At the end of the study, 68% of employed partial remitters versus 26% of employed complete remitters had been on sick leave in the previous six months (McNemar, $P < .001$). Employed partial remitters were, on average, three times more days absent from work with sickness than complete remitters (62.8 days, 95%CI = 46.7, 78.9 versus 20 days, 95%CI = 9.4, 30.9, respectively; paired *t*-student, $P < .001$). The work-related production loss due to PR was substantially greater than that due to CR. The indirect cost per patient in PR of a depressive episode was estimated at 3331 € over six months compared with 1066 €, the indirect cost per patient in CR (Table 3). Hence, the mean cost per patient in PR was 2300 € higher than for a patient in CR (paired *t*-student, $P < .001$).

3.7. Other results

On the other hand, only 30.1% of partial remitters and 22.6% of complete remitters were switched to another antidepressant during the study (McNemar, $P < 0.001$). The majority of switches were a combination with another antidepressant ($N = 20$; 41.7%) and switches from SSRI to SNRI ($N = 18$; 37.5%). At the end of six months, 46.1% ($N = 66$) of CR were on SNRI treatment, 27.3% ($N = 39$) were on SSRI, 17.5% ($N = 25$) were receiving a combination of antidepressants, 4.9% ($N = 7$) were taking a NaSSA and 4.2% ($N = 6$) other antidepressant treatment. Among partial remitters, 51.7% ($N = 74$) were on a SNRI treatment, 24.5% ($N = 35$) were on SSRI, 18.2% ($N = 26$) were receiving a combination of antidepressants and 5.6% ($N = 8$) were taking a NaSSA.

Most patients were taking the recommended dose for the given antidepressant (93.7% CR and 86.5% PR at baseline; 89.8% CR and 86.3% PR at six months). At six months, few patients were taking doses above (7.6% CR; 13.7% PR) or below (2.54% CR; 0.0% PR) the recommended ranges.

4. Discussion

To our knowledge, this is the first epidemiological study to provide evidence that patients in PR of an MDD episode have significant and persistent social and occupational functioning impairment compared with patients in CR after nine months of antidepressant treatment. This prospective study showed that, although patients in PR showed improvements in both clinical symptomatology and functioning from baseline, the SOFAS ratings for partial remitters still were not in the normal range over the six-month period of follow-up. In contrast, patients in CR were virtually symptom-free, and normal levels of functioning were sustained throughout the study in the majority of patients.

In addition, we found that the SOFAS and HAMD-17 scales were inversely correlated with high correlation coefficients,

Table 3
Indirect cost per patient (only working population) based on the number of sick-leave days over a six-month period.

	Employed patients (*N*)	Mean sick leave days per patient (CI 95%)	Average monthly salary per patient[a] (€)	Indirect cost per patient (€) (CI 95%)
Partial remission	72	62.8 (46.7–78.9)	1608.1	3331.1 (2475.3–4187.0)
Complete remission	72	20.1* (9.4–30.9)	1608.1	1066.5 (496.1–1636.9)

*$P < .001$ (paired *t*-test) versus partial remission; CI: confidence interval.
[a] The average monthly salary was obtained from the Spanish Quarterly Labor Cost Survey for the third quarter of 2007 (INE, 2007).

indicating that symptoms and functional improvements are significantly correlated. Throughout the follow-up period partial remitters showed improvement in both functioning and clinical symptoms. However, even after several months of treatment, a great percentage of partial remitters could not achieve normal levels of functioning. In contrast, complete remitters maintained both remission and normal functional level over six months with a slight increase in the percentage of patients achieving normal functioning throughout the study. In fact, our results indicate that being in CR of an MDD episode after three months of acute antidepressant treatment is strongly associated with normal social and occupational functioning levels in the longer term. Another factor associated with reaching normal functioning levels was showing a HAMD-17 score reduction throughout the study. Interestingly, Furukawa et al. (2001) [6] showed that functional recovery lagged behind clinical recovery in a sample of patients with mild depression, mainly first episodes. Paykel et al. (1971) [24] also reported long before that impairment in social functioning in depressed patients compared with controls persisted, even after improvement in clinical symptoms over the following eight months. Other studies describe also long-term functional impairment after depression in the majority of patients [17,22]. Although there appear to be a few indicators of a delay in functional improvement in relation to symptoms improvement, we can not establish a temporal relationship between both improvements. In summary, the findings presented here indicate that being in CR of an MDD episode after three months of acute antidepressant treatment is strongly associated with normal social and occupational functioning levels in the longer term.

Interestingly, although most partial remitters had not achieved normal functional levels after acute antidepressant treatment, only one third were switched to an alternative antidepressant therapy or combination during the following six months. This finding suggests that although full symptomatology and functional recovery after an MDD episode should be the goal of treatment, the former is still not pursued by physicians. In addition, the PR group had a longer history of dysthimic and personality disorders, suggesting that chronic symptomatology might be also influencing functional prognosis, and thus physicians should vigorously treat to remission.

According to Kennedy et al. (2007) [16], factors that may be associated with the persistence of psychosocial impairment even after clinical remission of depression include: the presence of ongoing residual symptoms at remission, neurocognitive deficits, comorbidity, misdiagnosis and treatment [16]. We propose that another possible explanation for the delay observed in functioning improvement, despite patients achieving clinical remission may be that the current definition of remission (HAMD: $\leq$7) does not best represent full remission according to patients' functioning. In fact, the definition of remission is not based on the resolution of both symptoms and functional impairments. There is evidence suggesting that the current symptom-based definition might be too narrow [30,31]. We performed a post hoc analysis, reported elsewhere [25], to study the sensitivity and specificity of the HAMD-17 as a measure for social and occupational functioning, to obtain the optimal cutoff point that predicts a normal functional level. The results showed that a score less than or equal to 5 on the HAMD-17 improved the level of agreement between a normal level of functioning and improvement in depressive symptoms. Our results are consistent with those reported by Zimmerman et al., suggesting that a lower cutoff point for the HAMD-17 should be used to best define remission according to psychosocial functioning [31].

Finally, in our sample more than half of employed partial remitters had been on sick leave compared with less than one third of complete remitters, and were three times more days absent from work than complete remitters. It should be noted, however, that absenteeism is driven by many causes other than depression and that it is sometimes difficult to attribute it only to a single cause. To our knowledge, these are the first data in Spain to show that PR of an MDD episode is associated with significantly greater increase in indirect costs (short-term sick leave) than CR. The cost difference resulting from sick leave was 2300 € ($P < .001$) over a six-month period. This finding is consistent with a previous study carried out in Sweden showing a sick-leave cost difference of 2500 € ($P = 0.020$) between non-remitting versus remitting patients [27].

There are several limitations to our study. First, as this is a naturalistic study, the data collection was designed to interfere to a lesser extend with the physician's normal course of work; therefore, biases associated with this type of design might have an effect on data-collecting (i.e. the use of assessment instruments and judgmental scales). Additionally, the inherent biases associated with the open-label nature of observational studies might have an effect on data collecting (i.e. experimenter bias). Second, some data may be affected by bias in patients' recollection of occasional sick-leave days. Third, an observational study cannot prove any causal relationships between PR, social and occupational functioning and costs, but only show associations. Other limitation is that at time of inclusion, patients were in PR or CR and were previously treated for 12 weeks ($\pm$ 2 weeks); that is, patients were included in the study during the course of the MDD episode and not in the acute phase of the episode. Therefore, this might have decreased the accuracy of the MDD diagnosis, not being as rigorous as in a clinical trial. However due to the naturalistic design of the study, both cohorts of patients in PR and CR reflects better the reality of clinical practice. Additionally, in order to minimize this possible bias, patients were required to have a history of at least one previous depression episode and the diagnosis of MDD was made by the investigator, who also was the treating psychiatrist. Since patients were included in the study during the course of the MDD episode and not in the acute phase, information regarding the HAMD score or other relevant information at the beginning or during the acute phase was not collected. Although this information would help to have a broader perspective of the study results, nevertheless the aim of the study was to prospectively evaluate functional impairment in patients that achieved PR versus those who achieved CR after acute antidepressant treatment. It was not the aim of the study to evaluate which factors are associated with achieving partial or CR. It should be mentioned that it would have been optimal to

include a self-reported global scale for functional disability, as a secondary measure to complement the SOFAS, and other measures of indirect costs apart from sick leave. Finally, another limitation of this study is that it is focused on short-term functional recovery and does not provide data on the full long-term association of PR and functioning.

5. Conclusion

This is the first study in Spain to show that PR of an MDD episode is associated with significant social and occupational functioning impairment, which persists even after nine months of antidepressant treatment. Being in PR is associated with a significantly greater increase in indirect costs (due to short-term sick leave) than CR. Our study has demonstrated that the SOFAS ratings, although greatly improved from baseline for partial remitters, still were not in the normal range despite clinical symptomatology improvement over a six-month period of follow-up. Our results underline the importance of treating the patient until achieving full remission from the depressive episode to improve, not only depressive symptoms, but also functional and health outcomes.

Acknowledgements

The authors gratefully acknowledge the contribution of Lorena Redondo (Lilly, Spain) and Amparo Valladares (Lilly, Spain) during the study and the preparation of the manuscript. We also thank the contribution made by the investigators of the study.

References

[1] Broadhead WE, Blazer DG, George LK, Tse CK. Depression, disability days, and days lost from work in a prospective epidemiologic survey. JAMA 1990;264:2524–8.
[2] Corey-Lisle PK, Nash R, Stang P, Swindle R. Response, partial response, and nonresponse in primary care treatment of depression. Arch Intern Med 2004;164:1197–204.
[3] De Lisio G, Maremmani I, Perugi G. Impairment of work and leisure in depressed outpatients. J Affect Disord 1986;10:79–84.
[4] Doraiswamy PM, Khan ZM, Donahue RM, Richard NE. Quality of life in geriatric depression: a comparison of remitters, partial responders, and nonresponders. Am J Geriatr Psychiatry 2001;9:423–8.
[5] Frank E, Prien RF, Jarrett RB, Keller MB, Kupfer DJ, Lavori PW, et al. Conceptualization and rationale for consensus definitions of terms in major depressive disorder. Remission, recovery, relapse, and recurrence. Arch Gen Psychiatry 1991;48:851–5.
[6] Furukawa TA, Takeuchi H, Hiroe T, Mashiko H, Kamei K, Kitamura T, et al. Symptomatic recovery and social functioning in major depression. Acta Psychiatr Scand 2001;103:257–61.
[7] Goldman HH, Skodol AE, Lave TR. Revising axis V for DSM-IV: a review of measures of social functioning. Am J Psychiatry 1992;149: 1148–56.
[8] Guy W. ECDEU Assessment Manual for Psychopharmacology, [Revised]. Rockville: National Institute of Mental Health, Dept of Health, Education, and Welfare publication (ADM); 1976, p. 76–338.
[9] Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960;23:56–62.
[10] Hamilton M. Development of a rating scale for primary depressive illness. Br J Soc Clin Psychol 1967;6:278–96.
[11] Hays RD, Wells KB, Sherbourne CD, Rogers W, Spritzer K. Functioning and well-being outcomes of patients with depression compared with chronic general medical illnesses. Arch Gen Psychiatry 1995;52:11–9.
[12] Hodgson TA, Meiners MR. Cost-of-illness methodology: a guide to current practices and procedures. Milbank Mem Fund Q Health Soc 1982;60:429–62.
[13] Judd LL, Akiskal HS, Maser JD, Zeller PJ, Endicott J, Coryell W, et al. Major depressive disorder: a prospective study of residual subthreshold depressive symptoms as predictor of rapid relapse. J Affect Disord 1998;50:97–108.
[14] Judd LL, Paulus MP, Wells KB, Rapaport MH. Socioeconomic burden of subsyndromal depressive symptoms and major depression in a sample of the general population. Am J Psychiatry 1996;153:1411–7.
[15] Keller MB. Past, present, and future directions for defining optimal treatment outcome in depression: remission and beyond. JAMA 2003;289: 3152–60.
[16] Kennedy N, Foy K, Sherazi R, McDonough M, McKeon P. Long-term social functioning after depression treated by psychiatrists: a review. Bipolar Disord 2007;9:25–37.
[17] Kocsis JH, Schatzberg A, Rush AJ, Klein DN, Howland R, Gniwesch L, et al. Psychosocial outcomes following long-term, double-blind treatment of chronic depression with sertraline vs placebo. Arch Gen Psychiatry 2002;59:723–8.
[18] Miller IW, Keitner GI, Schatzberg AF, Klein DN, Thase ME, Rush AJ, et al. The treatment of chronic depression, part 3: psychosocial functioning before and after treatment with sertraline or imipramine. J Clin Psychiatry 1998;59:608–19.
[19] Mintz J, Mintz LI, Arruda MJ, Hwang SS. Treatments of depression and the functional capacity to work. Arch Gen Psychiatry 1992;49:761–8.
[20] Nierenberg AA, Wright EC. Evolution of remission as the new standard in the treatment of depression. J Clin Psychiatry 1999;60:7–11.
[21] Opdyke KS, Reynolds CF, Frank E, Begley AE, Buysse DJ, Dew MA, et al. Effect of continuation treatment on residual symptoms in late-life depression: how well is ''well''? Depress Anxiety 1996–1997;4:312–9.
[22] Papakostas GI, Petersen T, Denninger JW, Tossani E, Pava JA, Alpert JE, et al. Psychosocial functioning during the treatment of major depressive disorder with fluoxetine. J Clin Psychopharmacol 2004;24:507–11.
[23] Paykel ES, Ramana R, Cooper Z, Hayhurst H, Kerr J, Barocka A. Residual symptoms after partial remission: an important outcome in depression. Psychol Med 1995;25:1171–80.
[24] Paykel ES, Weissman M, Prusoff BA, Tonks CM. Dimensions of social adjustment in depressed women. J Nerv Ment Dis 1971;152:158–72.
[25] Romera I, Delgado-Cohen H, Perez V, Menchon JM, Polavieja P, Yruretagoyena B, Gilaberte I. Optimal cutoff point to define remission by the Hamilton Rating Scale for Depression according to normal social and occupational functioning. Presented as a poster at the International Forum of Mood and Anxiety Disorders (IFMAD) 2007. Budapest.
[26] Salminen JK, Saarijärvi S, Raitasalo R. Depression and disability pension in Finland. Acta Psychiatr Scand 1997;95:242–3.
[27] Sobocki P, Ekman M, Agren H, Runeson B, Jönsson B. The mission is remission: health economic consequences of achieving full remission with antidepressant treatment for depression. Int J Clin Pract 2006;60:791–8.
[28] Spitzer RL, Gibbon M, Endicott J. Global Assessment Scale (GAS), Global Assessment of Functioning (GAF) Scale, Social and Occupational Functioning Assessment Scale (SOFAS). Mental Health Status, Functioning and Disability Measures. In: First MB, editor. Handbook of psychiatric measures,. . 1st ed, Washington DC, USA: American Psychiatric Association; 2000. p. 96–100.
[29] Wells KB, Stewart A, Hays RD, Burnam MA, Rogers W, Daniels M, et al. The functioning and well-being of depressed patients. Results from the Medical Outcomes Study. JAMA 1989;262:914–9.
[30] Zimmerman M, McGlinchey JB, Posternak MA, Friedman M, Boerescu D, Attiullah N. Discordance between self-reported symptom severity and psychosocial functioning ratings in depressed outpatients: implications for how remission from depression should be defined. Psychiatry Res 2006; 141:185–91.
[31] Zimmerman M, Posternak MA, Chelminski I. Is the cutoff to define remission on the Hamilton Rating Scale for Depression too high? J Nerv Ment Dis 2005;193:170–5.

Psychiatry Research 186 (2011) 133–137

Contents lists available at ScienceDirect

Psychiatry Research

journal homepage: www.elsevier.com/locate/psychres

Optimal cutoff point of the Hamilton Rating Scale for Depression according to normal levels of social and occupational functioning

Irene Romera [a,*], Víctor Pérez [b,1], José Manuel Menchón [c,2], Pepa Polavieja [a,3], Inmaculada Gilaberte [a,3]

[a] Clinical Research Department, Lilly, S.A., Avenida de la Industria, 30, Alcobendas E-28108, Madrid, Spain
[b] Department of Psychiatry, Hospital de Sant Pau i de la Santa Creu. C/Sant Antoni Maria Claret, 167. E-08025, Barcelona, CIBERSAM, Spain
[c] Department of Psychiatry, Hospital Universitari de Bellvitge. Feixa Llarga, sn. E-08907, Hospitalet de Llobregat, Barcelona, CIBERSAM, Spain

ARTICLE INFO

Article history:
Received 18 December 2009
Received in revised form 3 June 2010
Accepted 23 June 2010

Keywords:
Major depressive disorder
Remission
Social and occupational functioning

ABSTRACT

The main goal in the treatment of major depressive disorder (MDD) is to achieve remission, defined as the resolution of symptoms and the return to normal levels of functionality. However, the clinical assessment of remission is usually merely based on scores of symptomatic rating scales. One of the most widely used scales to measure remission is the HAM-D_{17}, in which remission is defined as a score ≤ 7. Nevertheless, several studies have shown that this cutoff could be too high when also functioning is considered. This is a post-hoc analysis of a 6-month prospective study, performed over a sample of 292 Spanish patients with MDD, in order to find the optimal cutoff in the HAM-D_{17} scale, considering normal levels of functionality, evaluated by the SOFAS; by means of plotting Receiver Operating Characteristics (ROC) curves. Our results show that a score of ≤ 5 maximized both sensitivity and specificity for identifying normal levels of functionality with respect to other scores, and thus agree with previous works, which suggest that a cutoff ≤ 7 might be too high to consider remission in patients with MDD, when normal levels of functioning are taken into account.

1. Introduction

In the last years, the main goal in the treatment of patients suffering major depressive disorder (MDD) has moved towards the achievement of remission, defined as the resolution of symptoms and the return to normal levels of functionality (Keller, 2003; Trivedi et al., 2006; Rush et al., 2009). This perspective responds to the results of several studies which have shown that patients who do not achieve remission have both an increased risk of relapse, and a shorter time to relapse (e.g., Thase et al., 1992; Paykel et al., 1995; Judd et al., 1998; Pintor et al., 2004). It also has been seen that those patients not achieving remission continue to experience functional impairment, and have poorer quality of life after treatment than remitters (Mintz et al., 1992; Thase et al., 1992). Furthermore, non-remitters have an increased risk and poorer prognosis in other conditions such as cardiovascular diseases, glycemic control in diabetes mellitus, or human immunodeficiency virus disease progression (Keller, 2003). Even more, very recently a greater decline in gray matter volume in unremitted compared with remitted MDD patients has been shown (Frodl et al., 2008).

However, although remission implies both the absence of symptoms and functional impairment, the clinical assessment of remission is usually merely based on scores of symptomatic rating scales such as the 17-item Hamilton Rating Scale for Depression (HAM-D17; Hamilton, 1960, 1967), which even if recently criticized Bagby et al. (2004) is still the gold standard (Bech et al., 2005; Carroll, 2005; Moller, 2008). Therefore, remission is currently merely evaluated by symptomatic rating scales where patient's functionality is not taken into account.

Based on the HAM-D_{17} scale, remission has been traditionally defined by scores from ≤ 12 to ≤ 6, although since 1991 there is a consensus on using a score of ≤ 7 (Frank et al., 1991). Nevertheless, several studies point out that a cutoff score of ≤ 7 might be too high to consider that a patient is in truly remission (e.g., Riso et al., 1997; Judd et al., 2000). On this basis, on 2006 the American College of Neuropsychopharmacology (ACNP) recommended both using scores of ≤ 7 or ≤ 5 (Rush et al., 2006; Moller, 2008). Moreover, Zimmerman et al. (2007) analyzed the heterogeneity in the symptoms and psychosocial impairment in patients classified as remitters (HAM-$D_{17} \leq 7$) and non-remitters (HAM-$D_{17} \geq 8$), showing that remitters are as heterogeneous as responders and, consequently, supporting the idea that a lower cutoff should be used to define remission.

Therefore, there is still controversy on which cutoff point better reflects the absence of not only symptoms but also functional impairment. However, little research has been performed regarding the association between the HAM-D_{17} score and patient's functioning. More specifically, scarce information is available regarding the

* Corresponding author. Tel.: +34 91 663 50 00; fax: +34 91 663 52 31.
E-mail addresses: romera_irene@lilly.com (I. Romera), vperez@hsp.santpau.es (V. Pérez), jmenchon@csub.scs.es (J.M. Menchón), polavieja_pepa@lilly.com (P. Polavieja), gilaberte_inmaculada@lilly.com (I. Gilaberte).
[1] Tel.: +34 93 291 90 00.
[2] Tel.: +34 93 260 76 00
[3] Tel.: +34 91 663 50 00; fax: +34 91 663 52 31.

0165-1781/$ – see front matter © 2010 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.psychres.2010.06.023

optimal HAM-D_{17} cutoff point in patients with MDD according to normal levels of social and occupational functioning. Therefore, the objective of the present work is to explore the optimal cutoff for the HAM-D_{17} scale in clinical practice, taking into account normal levels of patients' functionality, in a cohort of patients with MDD in total or partial remission, at the end of a 6-month follow-up period. Moreover, the correlation between functioning and clinical improvement will be explored throughout the 6-month prospective period.

2. Methods

2.1. Subjects

This is a post-hoc analysis of a 6-month prospective, multicentric, observational study (Romera et al., 2010), performed over 292 patients from 36 psychiatric consultation centers in Spain. Patients were ≥18 years old, with at least a prior MDD episode and a current MDD episode without psychotic traits, as defined by the Diagnostic and Statistical Manual of Mental Disorders (fourth edition; DSM-IV). At study entry, patients had to be in total (HAM-D_{17} ≤7) or partial (HAM-D_{17} >7 and ≤15) remission of the episode, after being previously treated for 12 (±2) weeks with acute antidepressant treatment. Patients were considered to be in total remission if they did not meet criteria for MDD, as defined by the DSM-IV, and had a HAM-D_{17} total score of ≤7. Patients were considered to be in partial remission if they did not meet criteria for MDD, as defined by DSM-IV, and had a HAM-D_{17} total score >7 and ≤15. Exclusion criteria were: (a) previous diagnosis of bipolar disorder, schizophrenia, or other psychotic disorder, (b) a current diagnosis of dysthymic disorder or adjustment disorder, and (c) HAM-D_{17} score >15.

The protocol of the study was approved by the local ethical review board of the Hospital Universitari de Bellvitge, according to the principles of the Declaration of Helsinki. All patients had received detailed information on the study, and had provided their written informed consent prior to their inclusion.

2.2. Study assessments

The primary efficacy variable was social and occupational functioning. Social and occupational functioning was measured by the Social and Occupational Functioning Assessment Scale (SOFAS; Goldman et al., 1992), which takes into account functional impairment caused by both physical limitations and mental problems. The SOFAS considers social and occupational functioning across a continuum that ranges from 100 (optimal functioning) to 1 (serious functional impairment). The severity of MDD was measured by the HAM-D_{17} scale (Hamilton, 1960, 1967; Riskind et al., 1987). The HAM-D_{17} is a gradual scale which ranges from 0 (no depression) to 52 (severe depression), taking into account symptoms related to mood, anxiety, sexual function, appetite, sleep, functional status, physical symptoms, hypochondriasis, diurnal variation, and general psychiatric distress. The severity of anxiety was measured by the Hamilton Anxiety Scale (HAM-A; Hamilton, 1959; Riskind et al., 1987), which is based on the presence and severity of 14 symptoms rated from 0 to 4. The HAM-A scale ranges from 0 (no anxiety) to 56 (severe anxiety).

Patients were evaluated at baseline, at 3 months, and at 6 months after their inclusion in the study. Sociodemographic data and MDD clinical history were collected at baseline, while efficacy variables were assessed at all visits. Work impairment was assessed at baseline. Absenteeism and self-reported disability (whether the patient was unable to carry out normal activities or did not get as much done as usual) were collected for patients with paid work and unpaid work (e.g. houseworkers), respectively (Mojtabai, 2001).

Patients were considered in relapse if they had an increase of ≥2 points in the Clinical Global Impression-Severity (CGI-S) score, and if they meet the criteria of MDD as defined by DSM-IV at their last visit. The CGI-S is a single-item rating of the clinician's assessment of the severity of the patient's symptoms. The severity score ranges from 1 (normal, not at all ill) to 7 (among the most extremely ill patients) Guy (1976) Patients were considered to have normal levels of functionality if they presented a SOFAS score of ≥80 (American Psychiatric Association, 2005).

2.3. Statistical analysis

Demographic and clinical data at baseline were described by means of percentages (qualitative variables), or mean ± standard deviation (quantitative variables).

In order to determine and compare the sensitivity and specificity of the HAM-D_{17} as an indicator of normal levels of functionality according to the SOFAS (SOFAS score ≥80) at 6 months, and obtain optimal cutoff scores of the HAM-D_{17} scale, we plotted receiver operating characteristic curves (ROC curves).

Optimal cutoff scores were determined by assessing the score which combined maximum sensitivity with optimal specificity. Validity coefficients (specificity, sensitivity, and positive and negative predictive values), as well as the area under the curve (AUC) using the trapezoidal rule and its associated asymptotic 95% confidence interval, were calculated. The AUC varies from 0.5 (no apparent accuracy) to 1.0 (perfect accuracy), representing the probability that a randomly chosen diseased subject is rated or ranked with greater suspicion than a randomly chosen non-diseased subject. Higher values of the AUC are achieved when the ROC curve moves towards the left and top boundaries of the ROC graph.

In addition, two more ROC curves for normal levels of functioning (SOFAS score ≥80) at 6 months were plotted using the HAM-D_6 subscale and the item 1 (depressed mood) of the HAM-D_{17} scale. The HAM-D_6 is a version of the HAM-D_{17} scale which measures depressed mood, guilt, work, retardation, psychic anxiety and somatic symptoms (Bech et al., 1981).

The correlation between social and occupational functioning (SOFAS) and MDD severity (HAM-D_{17} scale) improvement was assessed at baseline, 3 months, and 6 months, by means of the Pearson coefficient.

Rates of relapse throughout the follow-up were described in three different strata according to HAM-D_{17} cutoffs at baseline (≤5, 6–7, and 8–15). Comparisons between rates in each strata were made by means of Chi-square tests. Wilcoxon rank test was also used to compare the mean SOFAS score for patients scoring 0–5 or 6–7.

Since this is a post-hoc analysis, sample size calculation was based on the primary outcome of the main study, which was the evaluation of the differences in psychosocial functioning between the group of patients with partial remission of the MDD episode after 12 weeks of antidepressant treatment, and the group with complete remission (Romera et al., 2010).

3. Results

3.1. Baseline demographics and clinical characteristics

Demographic data and clinical history at baseline are shown in Table 1. Most patients were females (77%), with a mean age of 51 ± 15 years, and primary education (42%). Approximately half of the patients (51%) had no paid jobs.

The mean age for the first MDD episode was 37.8 ± 14.0 years, with a mean of 3.7 ± 3.8 preceding depression episodes. The most frequent prior diagnoses were adjustment disorders (16%) and anxiety disorders (13%). Regarding treatments, patients were mostly

Table 1
Baseline demographics and clinical characteristics.

	N = 292
Age (mean ± S.D., years)	50.50 ± 14.56
Gender, female *N* (%)	113 (77.4)
Education	
No education *N* (%)	22 (7.53)
Primary level *N* (%)	124 (42.47)
Secondary level *N* (%)	95 (32.53)
University level *N* (%)	51 (17.47)
Work	
Not paid *N* (%)	148 (50.68)
Self-reported disability *N* (%)	72 (48.65)
Days of self-reported disability, in the last 30 days (mean ± S.D.)	8.51 ± 11.12
Paid *N* (%)	144 (49.32)
Absenteeism in the last 3 months *N* (%)	95 (65.97)
Days of absence (mean ± S.D.)	31.97 ± 33.32
MDD episodes	
Age at first MDD episode (mean ± S.D., years)	37.84 ± 14.03
Number of previous depression episodes (mean ± S.D.)[a]	3.66 ± 3.82
Total duration of the current episode (mean ± S.D., weeks)	19.47 ± 11.46
History of previous psychiatric disorders	
At least one *N* (%)	90 (30.82)
Personality disorder *N* (%)	16 (5.48)
Dysthymic disorder *N* (%)	25 (8.56)
Adjustment disorder *N* (%)	46 (15.75)
Anxiety disorder *N* (%)	37 (12.67)
Previous antidepressant treatment[b]	
SSRI *N* (%)	110 (37.67)
SNRI *N* (%)	125 (42.81)
NaSSA *N* (%)	13 (4.45)
Other *N* (%)	6 (2.05)
Combination *N* (%)	38 (13.01)
Severity of depression according to Hamilton scales	
HAM-D_{17} mean total score (mean ± S.D.)	8.21 ± 4.34
HAM-A mean total score (mean ± S.D.)	10.32 ± 6.40
HAM-D_6 mean total score (mean ± S.D.)	4.48 ± 2.62

[a] Data missing from one subject.
[b] SSRI = selective serotonin reuptake inhibitor, NaSSA = noradrenergic and specific serotonergic antidepressant, SNRI = serotonin and norepinephrine reuptake inhibitor.

receiving serotonin and norepinephrine reuptake inhibitors (SNRIs, 43%), or selective serotonin reuptake inhibitors (SSRIs, 38%). At baseline, the mean HAM-D_{17} score was 8.2 ± 4.3, the mean HAM-A score was 10.3 ± 6.4, and the mean SOFAS score was 71.6 ± 14.6.

3.2. Social and occupational functioning and HAM-D_{17} score

Sensitivities and specificities for the various cutoffs were computed and a ROC curve (Fig. 1) was constructed to determine the best cutoff to choose.

The area under the ROC curve was 0.81 (CI 95%: 0.76–0.86). This value is close to one, which indicates that the HAM-D_{17} has high concurrent validity with functionality. According to the ROC curve, the cutoff level yielding the maximal sensitivity and specificity for predicting normal levels of functionality was a HAM-D_{17} score of 5. This point had a sensitivity of 75% and a specificity of 74%. The traditional cutoff HAM-D_{17} score of 7 yielded a sensitivity of 81% and specificity of 55%. Table 2 shows the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of the selected cutoff points. From the table we can see that the optimum cutoff which maximizes both sensitivity and specificity is a score of 5.

Mean SOFAS score for patients scoring 6–7 on the HAM-D17 was 79.5 (CI 95%: 76.7–82.3). For patients scoring 0–5, mean SOFAS score was 85.2 (CI 95%: 83.9–86.6). The difference between both groups was statistically significant ($P = 0.0002$), which indicates that patients with a scoring on the HAM-D17 ≤ 5 had better levels of functioning and are within the range that is considered as normal levels of functionality (SOFAS score ≥ 80).

As shown in Fig. 2, HAM-D_{17} score and social and occupational functioning, assessed by the SOFAS, were significantly inversely correlated at baseline (Pearson correlation coefficient $r = -0.62$; $P<0.0001$), at 3 months ($r = -0.62$; $P<0.0001$) and at 6 months ($r = -0.64$; $P<0.0001$). Thus, symptoms measured by the Hamilton explained approximately 38% of the variation in functioning.

Regarding relapse rates throughout the follow-up, few patients relapsed, and no differences were found neither with regard to a HAM-D_{17} cutoff score of 5 (6.7%, $n = 7$) vs 6–7 (9.52%, $n = 4$) at baseline ($P = 0.730$), nor for a HAM-D_{17} cutoff score of 7 (7.5%, $n = 11$) vs 8–15 (8.2%, $n = 12$) ($P = 1.000$).

3.3. Social and occupational functioning, HAM-D_6 and item 1 of the HAM-D_{17} scores

For the HAM-D_6 subscale, the area under the ROC curve was 0.82 (CI 95%: 0.76–0.87). This value indicates that the HAM-D_6 has high concurrent validity with functionality. The cutoff level yielding the maximal sensitivity and specificity for predicting normal levels of functionality was a HAM-D_6 score of 3. This point had a sensitivity of 82% and a specificity of 66%.

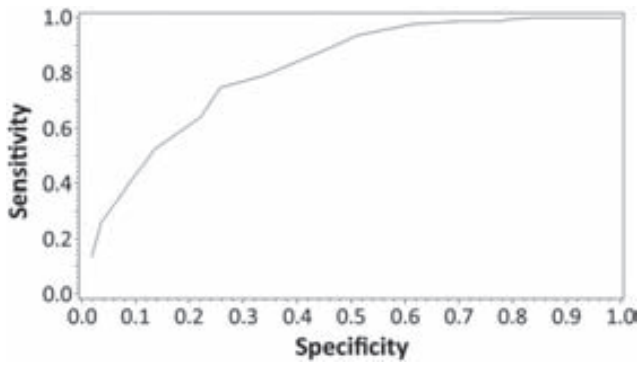


Fig. 1. Specificity and sensitivity ROC curve of the HAM-D_{17} score.

Table 2
Selected cutoff points with their sensitivities, specificities, positive predictive values (PPVs) and negative predictive values (NPVs), for predicting normal levels of functionality (SOFAS). $N = 284$.

HAM-D_{17} cutoff	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
2	38.4	91.7	88.3	47.8
5	74.6	74.3	82.5	64.3
7	88.1	55.0	76.1	74.1

For depressed mood, the AUC was 0.76 (CI 95%: 0.70–0.81), indicating less concurrent validity with functionality than with the HAM-D_6 or the HAM-D_{17} scales. The cutoff point that maximized both sensitivity and specificity for normal levels of functionality was zero. This point had a sensitivity of 66% and a specificity of 76%.

4. Discussion

In this observational study, we have analyzed 292 patients with MDD in partial or complete remission, to find the optimal cutoff point of the HAM-D_{17} scale that better predicts normal levels of social and occupational functioning, as assessed by the SOFAS. Specifically, our results show that a score of ≤5 maximized both sensitivity and specificity for identifying normal levels of functionality compared with other scores. Therefore, when not only symptoms but also social and occupational functional recovery are taken into account, the traditional cutoff point of the HAM-D_{17} could be considered too high; that is, having a HAMD score ≤7 does not necessarily imply normal levels of functionality. Consequently, when tracking the outcomes of depression, in addition to the evaluation of symptom, an assessment of patient's functional status would be desirable.

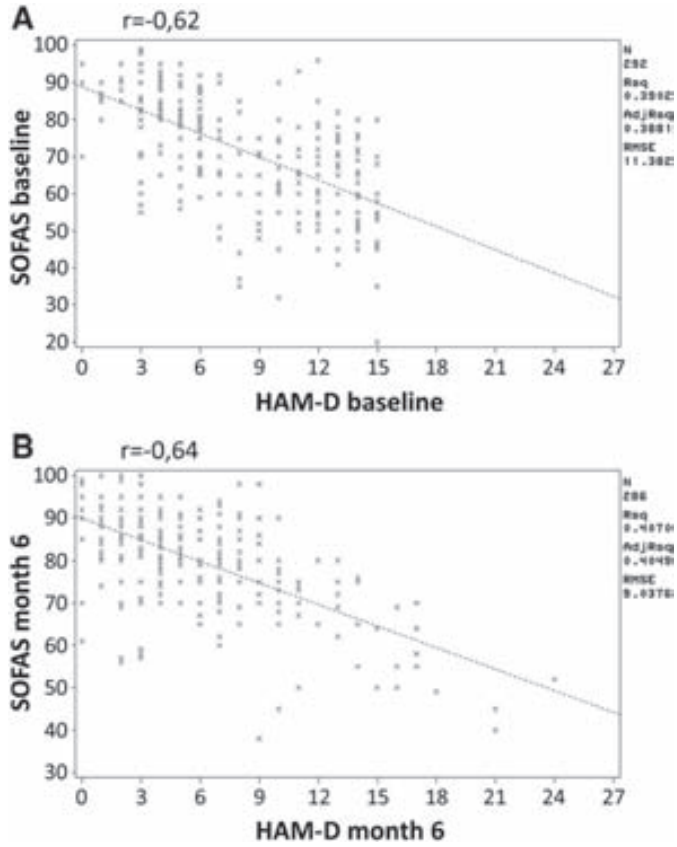


Fig. 2. Correlation between HAM-D_{17} and SOFAS scores at (A) baseline and (B) six months.

Our findings, thus, support the notion that a cutoff score of 7 on the HAM-D_{17} could be too high, as suggested by other investigators (Riso et al., 1997; Zimmerman et al., 2005, 2006b, 2007). Zimmerman et al. (2005) found that patients who scored ≤2 reported significantly less psychosocial impairment and better quality of life compared with patients scoring 3 through 7. Riso et al. (1997) found that a score of ≤6 predicted fewer dysfunctional attitudes and better global functioning compared with a score of 7 to 10. Similar results have been found with the Montgomery–Asberg Depression Rating Scale, where patients with lower scores (≤4 vs 5–9) reported better global functioning (Zimmerman et al., 2004); therefore, it is not surprising that lower cutoff scores are being used to report clinical outcomes (Wade et al., 2009). Finally and more specifically, a cutoff of ≤5 on the HAM-D_{17} is in accordance with the ACNP recommendations (Rush et al., 2006; Moller, 2008), which suggest using cutoff scores of ≤5 or ≤7; however, it is higher than the recommended by Zimmerman et al. (2005), ≤2.

In accordance with the main finding of our study, we have found that 24% of patients with a HAM-D_{17} score of ≤7 do not have normal levels of functioning at the end of the six-month follow-up period, as showed by a PPV of 76% for normal levels of functioning considering a cutoff of ≤7. Thus, a relevant percentage of patients who were considered to have recovered from MDD, according to the definition of remission used in clinical practice, were still suffering from it. That is, having a HAMD score of ≤7 does not necessarily imply having normal levels of functionality. As reported by Mintz et al. (1992), this gap between symptoms and functionality could be due to the fact that symptoms tend to improve considerably earlier than functionality, and that functional recovery lags behind clinical recovery (Furukawa et al., 2001). Therefore, had our study lasted more than 6 months, the percentage of patients in clinical remission but still suffering functional impairment could have been smaller. However, it must be taken into account that at baseline, the studied patients were already in complete or partial remission. Other factors that might be associated with the observed gap between symptoms and functionality were the presence of psychiatric or medical co-morbidity, poor levels of pre-morbid quality of life and functioning (Kennedy et al., 2007), or the presence of residual symptoms of depression with even a cutoff score of 7, as pointed out by other authors (Nierenberg et al., 1999).

When using a cutoff a score of ≤5, we have also found patients with functional impairment (17%, PPV: 83%); however, the proportion was lower than when using a cutoff score of ≤7. Thus, even if a cutoff score of ≤5 on the HAM-D17 is associated with a gap between clinical remission and the achievement of normal levels of functionality, this score was a better predictor of normal functioning than a cutoff of ≤7.

The optimal cutoff point for normal levels of functioning using the HAM-D_6 was 3. In previous studies, this cutoff point on the HAM-D_6 has been found to be equivalent to a cutoff point of 5 on the HAM-D_{17} (Ruhé et al., 2005). Therefore, this finding supports the consistency of the study results. The fact that patients scoring 0–5 on the HAM-D_{17} had significantly better levels of functionality, and were placed within the normal range, than patients scoring 6–7, also contributes to the consistency of the study results.

The practical clinical implication of our findings is the importance of measuring not only the clinical improvement, but also the functional improvement, when tracking the outcomes of patients suffering from depression. This is so because remission implies both the absence of MDD symptoms and of functional impairment. This approach is in accordance to that advocated by DSM-IV, which suggests that the symptoms of major depression should be evaluated in terms of their clinical impact on social, occupational or other important areas of functioning, and recommends the use of a global assessment by the clinicians (Goldman et al., 1992). This may be a challenge given that the use of functional scales, such as the SOFAS, is uncommon in the routine clinical practice, although from the patients' perspective, factors such as positive mental health (understood as optimism and self-confidence) or feeling like the normal self, are even more important than symptoms for the achievement of remission (Zimmerman et al., 2006a). A return to healthy functioning means that the patient is able to effectively perform in a wide range of areas, that is not only important according to patients' perception (Zimmerman et al., 2006a), but also is an indicator of a better prognosis, since it has been associated with lower risk of recurrence (Solomon et al., 2004).

Moreover, our results show that depression severity improvement, as measured by the HAM-D_{17} scale, is correlated with functioning improvement. This finding is in accordance with Trivedi et al. (2009) who, in a clinical trial, found a moderate correlation between change in the Sheehan Disability Scale and change in depressive symptoms. Zimmerman et al. (2008) also found that symptom severity, functional impairment from depression, and quality of life were significantly and highly inter-correlated. The degree of correlation between both scales is moderate to high, supporting the notion that symptoms and functioning, although correlated, are two different dimensions; which stress again the importance of patient's functioning evaluation.

Finally, we did not find a prognostic significance related to a HAM-D_{17} cutoff of ≤5, as no differences were found in relapse rates with regard to a given HAM-D_{17} cutoff at baseline (HAM-D_{17} cutoff ≤5 and ≤7). This could be explained by the low number of patients who experienced relapse. The low relapse rates could be partly explained by the short follow-up period.

Our study has several limitations. First, our results are based on an observational study, and therefore they are subjected to the inherent biases of open-label studies. However, a naturalistic design reflects the reality of clinical practice better than a clinical trial. Secondly, patients were included in the study during the course of the MDD episode, not in the acute phase. Consequently, information on the HAM-D_{17} and SOFAS scales at the beginning of the acute phase was not collected. Nevertheless, the aim of this work was to find the optimal cutoff of the HAM-D_{17} taking into account normal levels of functionality, so this limitation should not undermine our results. Thirdly, although a semi-structured assessment for the diagnosis of MDD was not used, in order to minimize this possible bias, patients were required to have a history of at least one previous depression episode, and the diagnosis of MDD, based on DSM-IV criteria, was made by the investigator, who also was the treating psychiatrist. Fourthly, in order to put the results into practice, it needs to be taken into account that the sensitivity and specificity of the HAM-D_{17} as an indicator of normal levels of functionality, were assessed at a specific time point, six months after the achievement of remission. Fifthly, we lack records on the social and occupational functioning of patients prior to their first and current MDD episode, that is, pre-morbid levels of functionality are not known. Sixthly, no reliability of the assessments was collected. Finally, our sample was composed only by Spanish patients, most of them females around 50 years old, which might limit the generalization of our results to other samples of different ethnic and demographic characteristics.

In conclusion, we have found that a cutoff of ≤5 on the HAM-D_{17} scale is a better predictor of normal levels of social and occupational functioning than other scores. The results of this study support the conclusions of previous works which suggest that a cutoff of ≤7 might be too high to consider remission in patients with MDD, when normal levels of functioning are taken into account. Consequently, to fully understand the patient status, when tracking the outcomes of depression, the inclusion of functioning assessment would be desirable.

Acknowledgements

The authors would like to thank all the investigators and patients who agreed to participate in this study.

We also thank the Department of Medical Writing, Infociencia (RPS Group), for assisting with the editing of the manuscript; and Ígor Martín from Chiltern International Inc. for his support with the statistical analysis.

This study was funded by Eli Lilly and Company.

References

American Psychiatric Association, 2005. Mental Health Status, Functioning and Disability Measures. In: Handbook of psychiatric measures. Washington.

Bagby, R.M., Ryder, A.G., Schuller, D.R., Marshall, M.B., 2004. The Hamilton Depression Rating Scale: has the gold standard become a lead weight? The American Journal of Psychiatry 161, 2163–2177.

Bech, P., Allerup, P., Gram, L.F., Reisby, N., Rosenberg, R., Jacobsen, O., Nagy, A., 1981. The Hamilton depression scale. Evaluation of objectivity using logistic models. Acta Psychiatrica Scandinavica 63, 290–299.

Bech, P., Engelhardt, N., Evans, K.R., Gibertini, M., Kalali, A.H., Kobak, K.A., Lipsitz, J.D., Williams, J.B.W., Pearson, J.D., Rothman, M., 2005. Why the Hamilton Depression Rating Scale endures. The American Journal of Psychiatry 162, 2396.

Carroll, B.J., 2005. Why the Hamilton Depression Rating Scale endures. The American Journal of Psychiatry 162, 2395–2396.

Frank, E., Prien, R.F., Jarrett, R.B., Keller, M.B., Kupfer, D.J., Lavori, P.W., Rush, A.J., Weissman, M.M., 1991. Conceptualization and rationale for consensus definitions of terms in major depressive disorder. Remission, recovery, relapse, and recurrence. Archives of General Psychiatry 48, 851–855.

Frodl, T.S., Koutsouleris, N., Bottlender, R., Born, C., Jäger, M., Scupin, I., Reiser, M., Möller, H.J., Meisenzahl, E.M., 2008. Depression-related variation in brain morphology over 3 years: effects of stress? Archives of General Psychiatry 65, 1156–1165.

Furukawa, T.A., Takeuchi, H., Hiroe, T., Mashiko, H., Kamei, K., Kitamura, T., Takahashi, K., 2001. Symptomatic recovery and social functioning in major depression. Acta Psychiatrica Scandinavica 103, 257–261.

Goldman, H.H., Skodol, A.E., Lave, T.R., 1992. Revising Axis V for DSM-IV: a review of measures of social functioning. American Journal of Psychiatry 149, 1148–1156.

Guy, W., 1976. ECDEU Assessment Manual for Psychopharmacology. Revised. National Institute of Mental Health, Rockville. p. 76–338.

Hamilton, M., 1959. The assessment of anxiety states by rating. British Journal of Psychology 32, 50–55.

Hamilton, M., 1960. A rating scale for depression. Journal of Neurology, Neurosurgery and Psychiatry 23, 56–62.

Hamilton, M., 1967. Development of a rating scale for primary depressive illness. The British Journal of Social and Clinical Psychology 6, 278–296.

Judd, L.L., Akiskal, H.S., Maser, J.D., Zeller, P.J., Endicott, J., Coryell, W., Paulus, M.P., Kunovac, J.L., Leon, A.C., Mueller, T.I., Rice, J.A., Keller, M.B., 1998. Major depressive disorder: a prospective study of residual subthreshold depressive symptoms as predictor of rapid relapse. Journal of Affective Disorders 50, 97–108.

Judd, L.L., Paulus, M.J., Schettler, P.J., Akiskal, H.S., Endicott, J., Leon, A.C., Maser, J.D., Mueller, T., Solomon, D.A., Keller, M.B., 2000. Does incomplete recovery from first lifetime major depressive episode herald a chronic course of illness? The American Journal of Psychiatry 157, 1501–1504.

Keller, M.B., 2003. Past, present, and future directions for defining optimal treatment outcome in depression: remission and beyond. Journal of the American Medical Association 289, 3152–3160.

Kennedy, N., Foy, K., Sherazi, R., McDonough, M., McKeon, P., 2007. Long-term social functioning after depression treated by psychiatrists: a review. Bipolar Disorders 9, 25–37.

Mintz, J., Mintz, L.I., Arruda, M.J., Hwang, S.S., 1992. Treatments of depression and the functional capacity to work. Archives of General Psychiatry 49, 761–768 (Erratum published in 1993, Archives of General Psychiatry 50, 241.).

Mojtabai, R., 2001. Residual symptoms and impairment in major depression in the community. The American Journal of Psychiatry 158, 1645–1651.

Moller, H.J., 2008. Outcomes in major depressive disorder: the evolving concept of remission and its implications for treatment. The World Journal of Biological Psychiatry 9, 102–114.

Nierenberg, A.A., Keefe, B.R., Leslie, V.C., Alpert, J.E., Pava, J.A., Worthington 3rd, J.J., Rosenbaum, J.F., Fava, M., 1999. Residual symptoms in depressed patients who respond acutely to fluoxetine. The Journal of Clinical Psychiatry 60, 221–225.

Paykel, E.S., Ramana, R., Cooper, Z., Hayhurst, H., Kerr, J., Barocka, A., 1995. Residual symptoms after partial remission: an important outcome in depression. Psychological Medicine 25, 1171–1180.

Pintor, L., Torres, X., Navarro, V., Matrai, S., Gastó, C., 2004. Is the type of remission after a major depressive episode an important risk factor to relapses in a 4-year follow up? Journal of Affective Disorders 82, 291–296.

Riskind, J.H., Beck, A.T., Brown, G., Steer, R.A., 1987. Taking the measure of anxiety and depression. Validity of the reconstructed Hamilton scales. Journal of Nervous and Mental Disease 175, 474–479.

Riso, L.P., Thase, M.E., Howland, R.H., Friedman, E.S., Simons, A.D., Tu, X.M., 1997. A prospective test of criteria for response, remission, relapse, recovery, and recurrence in depressed patients treated with cognitive behavior therapy. Journal of Affective Disorders 43, 131–142.

Romera, I., Pérez, V., Menchón, J.M., Delgado-Cohen, H., Polavieja, P., Gilaberte, I., 2010. Social and occupational functioning impairment in patients in partial versus complete remission of a major depressive disorder episode. A six-month prospective epidemiological study. European Psychiatry 25, 58–65.

Ruhé, H.G., Dekker, J.J., Peen, J., Holman, R., de Jonghe, F., 2005. Clinical use of the Hamilton Depression Rating Scale: is increased efficiency possible? A post hoc comparison of Hamilton Depression Rating Scale, Maier and Bech subscales, Clinical Global Impression, and Symptom Checklist-90 scores. Comprehensive Psychiatry 46, 417–427.

Rush, A.J., Kraemer, H.C., Sackeim, H.A., Fava, M., Trivedi, M.H., Frank, E., Ninan, P.T., Thase, M.E., Gelenberg, A.J., Kupfer, D.J., Regier, D.A., Rosenbaum, J.F., Ray, O., Schatzberg, A.F., Task Force, A.C.N.P., 2006. Report by the ACNP Task Force on response and remission in major depressive disorder. Neuropsychopharmacology 31, 1841–1853.

Rush, A.J., Warden, D., Wisniewski, S.R., Fava, M., Trivedi, M.H., Gaynes, B.N., Nierenberg, A.A., 2009. STAR*D: revising conventional wisdom. CNS Drugs 23, 627–647.

Solomon, D.A., Leon, A.C., Endicott, J., Coryell, W.H., Li, C., Fiedorowicz, J.G., Keller, M.B., 2004. Psychosocial impairment and recurrence of major depression. Comprehensive Psychiatry 45, 423–430.

Thase, M.E., Simons, A.D., McGeary, J., Cahalane, J.F., Hughes, C., Harden, T., Friedman, E., 1992. Relapse after cognitive behavior therapy of depression: potential implications for longer courses of treatment. The American Journal of Psychiatry 149, 1046–1052.

Trivedi, M.H., Rush, A.J., Wisniewski, S.R., Nierenberg, A.A., Warden, D., Ritz, L., Norquist, G., Howland, R.H., Lebowitz, B., McGrath, P.J., Shores-Wilson, K., Biggs, M.M., Balasubramani, G.K., Fava, M., STAR*D Study Team, 2006. Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: implications for clinical practice. The American Journal of Psychiatry 163, 28–40.

Trivedi, M.H., Corey-Lisle, P.K., Guo, Z., Lennox, R.D., Pikalov, A., Kim, E., 2009. Remission, response without remission, and nonresponse in major depressive disorder: impact on functioning. International Clinical Psychopharmacology 24, 133–138.

Wade, A.G., Schlaepfer, T.E., Andersen, H.F., Kilts, C.D., 2009. Clinical milestones predict symptom remission over 6-month and choice of treatment of patients with major depressive disorder (MDD). Journal of Psychiatric Research 43, 568–575.

Zimmerman, M., Posternak, M.A., Chelminski, I., 2004. Defining remission on the Montgomery–Asberg depression rating scale. The Journal of Clinical Psychiatry 65, 163–168.

Zimmerman, M., Posternak, M.A., Chelminski, I., 2005. Is the cutoff to define remission on the Hamilton Rating Scale for Depression too high? The Journal of Nervous and Mental Disease 193, 170–175.

Zimmerman, M., McGlinchey, J.B., Posternak, M.A., Friedman, M., Attiullah, N., Boerescu, D., 2006a. How should remission from depression be defined? The depressed patient's perspective. The American Journal of Psychiatry 163, 148–150.

Zimmerman, M., McGlinchey, J.B., Posternak, M.A., Friedman, M., Boerescu, D., Attiullah, N., 2006b. Discordance between self-reported symptom severity and psychosocial functioning ratings in depressed outpatients: implications for how remission from depression should be defined. Psychiatry Research 141, 185–191.

Zimmerman, M., Posternak, M.A., Chelminski, I., 2007. Heterogeneity among depressed outpatients considered to be in remission. Comprehensive Psychiatry 48, 113–117.

Zimmerman, M., McGlinchey, J.B., Posternak, M.A., Friedman, M., Boerescu, D., Attiullah, N., 2008. Remission in depressed outpatients: more than just symptom resolution? Journal of Psychiatric Research 42, 797–801.

BMC Psychiatry

RESEARCH ARTICLE Open Access

Residual symptoms and functioning in depression, does the type of residual symptom matter? A post-hoc analysis

Irene Romera[1,2*], Víctor Pérez[3], Antonio Ciudad[1], Luis Caballero[4], Miguel Roca[5], Pepa Polavieja[1] and Inmaculada Gilaberte[1]

Abstract

Background: The degrees to which residual symptoms in major depressive disorder (MDD) adversely affect patient functioning is not known. This post-hoc analysis explored the association between different residual symptoms and patient functioning.

Methods: Patients with MDD who responded (≥50% on the 17-item Hamilton Rating Scale for Depression; HAMD-17) after 3 months of treatment (624/930) were included. Residual core mood-symptoms (HAMD-17 core symptom subscale ≥1), residual insomnia-symptoms (HAMD-17 sleep subscale ≥1), residual anxiety-symptoms (HAMD-17-anxiety subscale ≥1), residual somatic-symptoms (HAMD-17 Item 13 ≥1), pain (Visual Analogue Scale ≥30), and functioning were assessed after 3 months treatment. A stepwise logistic regression model with normal functioning (Social and Occupational Functioning Assessment Scale ≥80) as the dependent variable was used.

Results: After 3 months, 59.5% of patients (371/624) achieved normal functioning and 66.0% (412/624) were in remission. Residual symptom prevalence was: core mood symptoms 72%; insomnia 63%; anxiety 78%; and somatic symptoms 41%. Pain reported in 18%. Factors associated with normal functioning were absence of core mood symptoms (odds ratio [OR] 8.7; 95% confidence interval [CI], 4.6–16.7), absence of insomnia symptoms (OR 1.8; 95% CI, 1.2–2.7), episode length (4–24 weeks vs. ≥24 weeks [OR 2.0; 95% CI, 1.1–3.6]) and better baseline functioning (OR 1.0; 95% CI, 1.0–1.1). A significant interaction between residual anxiety symptoms and pain was found (p = 0.0080).

Conclusions: Different residual symptoms are associated to different degrees with patient functioning. To achieve normal functioning, specific residual symptoms domains might be targeted for treatment.

Keywords: Residual symptoms, Major depression, Functioning

Background

Residual symptoms of depression cause significant functional impairment [1,2]. This has been reported in patients who respond but are not remitters, partial remitters [1,2], and even in remitters (typically defined as a score of ≤7 on the 17-item Hamilton Depression Rating scale [HAMD-17]) with residual symptoms [2]. Residual symptoms are also associated with persistent functional impairment [1]. However, little is known about the role of specific residual symptom domains, such as core symptoms, symptoms of anxiety, somatic symptoms, and non-painful symptoms.

Most research in patients with residual symptoms has focused on the relationship between residual symptoms and depressive relapse. Several studies have shown an increased risk of relapse [3,4] and rapid relapse [5] in patients with residual symptoms after response without remission. A posthoc analysis from the Sequenced Treatment Alternatives to Relieve Depression [6] study showed that a greater number of residual symptom domains were associated with a higher probability of relapse in full symptomatic remitters. Although a few studies have evaluated the impact of residual symptoms

* Correspondence: romera_irene@lilly.com
[1]Department of Clinical Research Lilly, S.A. Avenida de la Industria 30, 28108, Alcobendas, Spain
[2]Autonomous University of Barcelona, Barcelona, Spain
Full list of author information is available at the end of the article

on functional impairment [1,2,7,8], to our knowledge, no published studies have examined the specific role of each residual symptom domain on functional impairment. This is definitely an area worthy of investigation, since the aim of treating depression is not only to achieve clinical remission, but also to return the patient to previous levels of functioning [9]. Knowledge of which residual symptom domains are associated with significant functional impairment and, to what degree would assist physicians in the implementation of specific strategies and treatments to increase the chances of achieving normal or previous levels of functioning.

The aim of this posthoc investigation was to assess the association of specific residual symptoms (core mood, insomnia, anxiety, somatic, and pain) with patient functioning in a large group of patients with an episode of major depressive disorder (MDD) who responded after 3 months of acute antidepressant treatment in routine clinical practice. Our hypothesis was that the strength of the association between residual symptoms and functioning would differ depending on the type of residual symptom.

Methods

This study is a post-hoc analysis done on a group of MDD patients who responded (improvement of ≥50% on the HAMD-17) after 3 months of acute treatment (n = 624). The analysis of the association between residual symptoms and functioning was done at three months of acute treatment. The source of data was based on a 1-year prospective observational study of a cohort of 930 outpatients with an index MDD episode [10]. As a non-interventional study, the patients were treated according to everyday clinical routine. The protocol was approved by the ethical review board of the Hospital Puerta de Hierro in Madrid, Spain, and all patients provided written informed consent before their inclusion in the study.

Participants

As described in detail elsewhere [10], adult outpatients with nonpsychotic MDD, single or recurrent episode, according to DSM-IV-TR® [11] were included. Patients had a baseline total score of ≥15 on the HAMD-17) [12] and at least a moderate (≥4) baseline score on the Clinical Global Impression-Severity (CGI-S) scale [13]. Patients suffering from Axis I main psychiatric disorder, dementia, Alzheimer's disease, organic brain syndrome, or cognitive impairment were excluded from the study.

Patients from this study who responded (improvement of ≥50% on the HAMD-17) after 3 months of acute antidepressant treatment were included in the present analysis.

Measures and definitions

The HAMD-17 was used to assess the severity of depression and its improvement. Remission was defined as a HAMD-17 score of ≤7 and a response as an improvement of 50% or more from the baseline score. Functioning was measured using the Social and Occupational Functioning Assessment Scale (SOFAS) [14], a 100-point single-item scale used to indicate the individual's level of social and occupational functioning across a continuum ranging from a state of optimum functioning to a state of important functional impairment. It measures only the level of social and occupational functioning without taking symptoms into account. Thus, a value of 1 represents the hypothetically most impaired individual and 100 the hypothetically healthiest individual. It is completed by a clinician using information from any clinical source. The two highest ranges on the SOFAS, 81–90 and 91–100, describe individuals who not only are without significant psychopathology, but who also exhibit many traits often considered to be components of positive mental health. A SOFAS score ≥80 was used to define normal levels of functioning [15]. The baseline and 3-month follow-up visits were included in this analysis.

Based on Dombrovski [16], we defined the presence of residual core mood symptoms as a score of 1 or more on the HAMD-17 core symptom subscale (depressed mood [Item 1], guilt [Item 2], suicide [Item 3], and anergia/anhedonia [Item 7]). The presence of residual insomnia symptoms was defined as a score of 1 or more on the HAMD-17 sleep subscale insomnia items (early [Item 4], middle [Item 5], and late [Item 6]). The presence of residual anxiety symptoms was defined as a score of 1 or more on the HAMD-17 anxiety subscale (agitation [Item 9], psychic anxiety [Item 10], somatic anxiety [Item 11], and hypochondriasis [Item 15]), and of residual somatic symptoms as a score of 1 or more for item 13 of the HAMD-17.

The Visual Analog Scale (VAS) for Pain was used to assess pain [17], defining the presence of pain as a VAS-overall pain ≥30 mm, which includes patients with at least moderate pain, and had been previously used for the identification of clinically significant pain [18]. The visual analog scale for pain is an instrument widely used in research studies to measure the level of pain. Its simplicity, reliability, and validity, make the VAS the optimal tool for describing pain [19,20]. Pain was measured by the VAS- overall pain, where the patient scores on a 100 point scale the level of overall pain in the last week.

Analysis

Demographic and clinical data at baseline were described by means of percentages (qualitative variables) or mean ± standard deviation (quantitative variables).

A stepwise logistic regression model was developed to evaluate the association between the residual symptom domains and patient functioning, with a normal level of functioning after 3 months of antidepressant treatment (SOFAS total score ≥80) as the dependent variable, and the following factors as the independent variables in the initial model: Age as a continuous variable, gender, marital status, working status, education status, baseline functioning (SOFAS score), baseline depression severity (HAMD-17), presence of previous episodes of depression, medical co-morbidities, length of current episode, residual symptoms at 3 months (core mood symptoms, insomnia symptoms, anxiety symptoms, somatic symptoms), and pain at 3 months. All the independent variables were included in a full model and then removed stepwise by backward selection (threshold for the p-value = 0.05). Interactions between variables were tested at 3 months (likelihood ratio). Only patients with complete information on the variables previously described were included in the model (n = 600). The reduced model was reported in terms of odds ratios (OR) and their 95% confidence intervals (CI); the fit of the final model was assessed using the Hosmer-Lemeshow goodness-of-fit test [21].

Receiver operating characteristics curves were plotted to determine and compare the sensitivity and specificity of the residual symptom domains and of the pain, as indicators of normal levels of functioning according to the SOFAS (SOFAS score ≥80) after 3 months of treatment. Areas under the curve (AUC) using the trapezoidal rule and their associated asymptotic 95% CIs were calculated. The AUC varies from 0.5 (no apparent accuracy) to 1.0 (perfect accuracy). SAS 9.2 for Windows (SAS Institute Inc., USA) was used for the statistical analysis.

Results

Patient disposition, demographics, and clinical characteristics

Of the evaluable sample (N = 930), 624 patients responded to antidepressant treatment and were therefore included in the present analysis. Table 1 shows the socio-demographic and clinical characteristics of the study sample of responders.

Residual symptom prevalence

After 3 months of acute antidepressant treatment, the most frequent residual symptom was anxiety in 78.2% of patients (95% CI, 74.8–81.4), followed by core mood symptoms in 72.1% (95% CI, 68.4–75.6), residual insomnia in 63.0% (95% CI, 59.1–66.8) and somatic symptoms in 41.3% (95% CI, 37.4–45.3). Pain was reported in 18.4% (95% CI, 15.5–21.7) of patients (Figure 1A). The severity of the residual symptoms and pain was mild (Table 2).

Table 1 Baseline demographic and clinical characteristics

Characteristics	N = 624
Age, years, mean (SD)	47.6 (13.8)
Gender, n (%)	
Women	408 (65.4)
Ethnicity, n (%)	
Caucasian	611 (97.9)
Marital status, n (%)	
Married	379 (60.7)
Single	132 (21.1)
Other[1]	113 (18.1)
Education, n (%)	
Illiterate	12 (1.9)
Basic school education	252 (40.4)
High school/higher education	316 (50.6)
Employment status, n (%)	
Active	264 (42.3)
Not working (unemployed or sick leave)	148 (23.7)
Other[2]	212 (34.0)
Patients with medical comorbidity, n (%)	339 (54.3)
Family psychiatric history, n (%)	221 (35.4)
Number of previous episodes, mean (SD)	2.6 (2.5)
Patients with 1st episode, n (%)	280 (44.9)
Age at first episode of depression, mean (SD)	40.5 (14.0)
Current depressive episode:	
Length, mean weeks (SD)	13.9 (23.5)
Chronicity ≥2 years, n (%)	38 (6.1)
HAMD-17 total score, mean (SD)	24.6 (5.7)
Residual symptoms, mean (SD)	
Core mood[3]	8.7 (2.3)
Insomnia[4]	3.9 (1.4)
Anxiety[5]	6.2 (2.2)
Somatic[6]	1.1 (0.6)
VAS-overall pain, total score (mean)	41.4 (28.2)
Monotherapy, n (%)	550 (88.1)
SSRI	145 (26.4)
SNRI	387 (70.3)
Tricyclic antidepressants	6 (1.1)
Others	12 (2.2)
Combination of antidepressants, n (%)	74 (11.9)

MDD = Major depressive disorder; SSRI = Selective serotonin reuptake inhibitor; SNRI = Serotonin-norepinephrine reuptake inhibitor; SD = Standard deviation; VAS = Visual Analog Scale; [1]Widowed, separated, divorced and other; [2]Student, housekeeping, retired, disabled worker; [3]depressed mood [Item 1], guilt [Item 2], suicide [Item 3], and anergia/anhedonia [Item 7] of the HAMD-17; [4]early [Item 4], middle [Item 5], and late insomnia [Item 6] of the HAMD-17; [5]agitation [Item 9], psychic anxiety [Item 10], somatic anxiety [Item 11], and hypochondriasis [Item 15] of the HAMD-17; [6]item 13 of the HAMD-17.

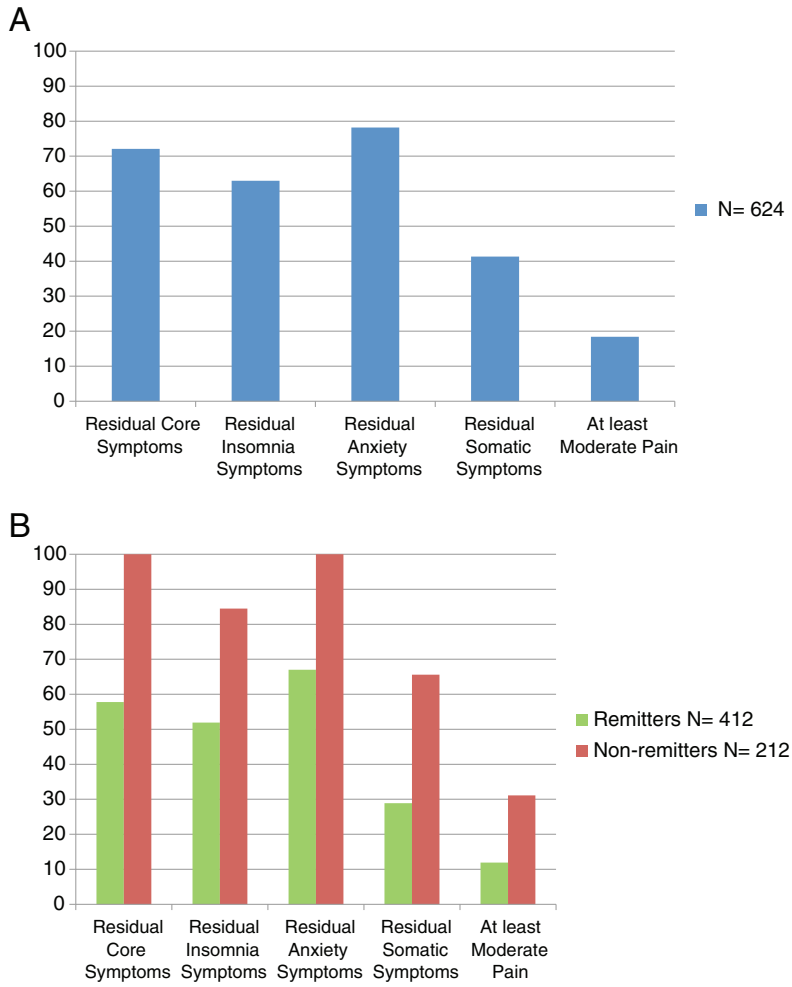


Figure 1 A Prevalence of residual symptoms domains and pain. All patients, N = 624. **B** Prevalence of residual symptoms domains and pain, based on remission (HAMD-17 ≤7) N = 412, or non-remission (HAMD-17 >7) N = 212.

After 3 months treatment, 66.0% (412/624) of the patients were in remission (HAMD-17 ≤7). Figure 1B shows the prevalence of residual symptoms by remission status at 3 months. About 90% of remitters (88.3%; 95% CI, 84.8–91.3) had residual symptoms from at least one of the domains studied.

Table 2 Residual symptoms, pain and HAMD-17 mean scores after 3 months of acute treatment, N = 624

Residual symptom	Mean (SD)
Core mood	1.8 (1.6)
Anxiety	1.8 (1.4)
Insomnia	1.0 (0.9)
Somatic	0.5 (0.6)
Pain	16.0 (18.4)
HAMD-17 total score	6.0 (3.8)

SD = Standard deviation.

Residual symptoms and patient functioning

More than half of the patients (59.4%, 371/624) had a normal level of functioning. Factors associated with normal functioning were absence of core mood symptoms (OR 8.7; 95% CI, 4.6–16.7), absence of insomnia symptoms (OR 1.8; 95% CI, 1.2–2.7), shorter episode length (4–24 weeks vs. ≥24 weeks [OR 2.0; 95% CI, 1.1–3.6]) and better baseline functioning (OR 1.0; 95% CI, 1.0–1.1). A significant interaction was found between residual anxiety symptoms and pain (p = 0.0080). The absence of pain increased the chance of normal functioning in either the absence (OR 21.7; 95% CI, 3.5–132.5) or presence of residual anxiety (OR 1.7; 95% CI, 1.0–2.8). However, the absence of residual anxiety was found to increase the chance of normal functioning only if pain was not present (OR 5.2; 95% CI, 2.4.–11.3) (Table 3). Demographic variables, physical co-morbidities, baseline depression severity, previous depression episodes and residual somatic symptoms were not significantly related to functioning (Table 3).

Table 3 Association between residual symptoms domains, pain and functioning

	Odds Ratio	95% Wald Confidence Limits	
Age	0.990	0.975	1.005
Gender (male vs. female)	1.356	0.886	2.076
Academic degree (high vs. other)	1.580	0.949	2.629
Baseline functioning level (SOFAS)	1.049	1.031	1.067
Episode length (4–24 weeks vs. ≥ 24 weeks)	2.008	1.127	3.579
Episode lenght (≤4 weeks vs. ≥24 weeks)	2.138	1.145	3.992
Absence of residual core mood symptoms	8.728	4.553	16.730
Absence of residual insomnia symptoms	1.796	1.175	2.744
Absence of residual anxiety symptoms and absence of pain	5.257	2.445	11.300
Absence of residual anxiety symptoms and presence of pain	0.412	0.073	2.341
Absence of pain and absence of residual anxiety symptoms	21.669	3.544	132.498
Absence of pain and presence of residual anxiety symptoms	1.700	1.025	2.819

Logistic regression model.
SOFAS = Social and Occupational Functioning Assessment Scale;
Dependent variable: normal level of functioning (SOFAS total score ≥80) after 3 months of antidepressant treatment.

The AUC for the residual core mood symptoms was 0.84 (95% CI, 0.80–0.87). Lower AUCs were found for the other residual symptom domains and pain: anxiety 0.75 (95% CI, 0.71–0.78); pain 0.73 (95% CI, 0.69–0.77); insomnia 0.65 (95% CI, 0.60–0.69); and residual somatic symptoms 0.62 (95% CI, 0.58–0.66).

Discussion

This study evaluated the relationship between patient functioning and specific residual symptom domains (core mood, insomnia, anxiety, somatic symptoms) and pain symptoms in a large group of patients with MDD who responded after receiving acute treatment. Anxiety was the most prevalent residual symptom, followed by core mood symptoms. The strength of the association between the residual symptom domains studied and patient functioning differed depending on the type of symptoms. A more marked association was found for residual core mood symptoms. Residual insomnia was less strongly related to patient functioning, and residual somatic symptoms were not associated.

To our knowledge, this is the first study to investigate the role of specific residual symptoms on patient functioning in MDD. Most publications about residual symptoms in MDD focus on their description and on their relationship to relapse and recurrence of depression [6,22-27]. More recent publications have evaluated their relationship to time to remission [6,28]. Few studies have specifically investigated the relationship between residual symptoms and functional impairment, but instead have focused on the overall impact of these symptoms on functioning without a separate analysis of the type of residual symptom [1,8,29].

As reported previously, residual symptoms are very common after acute treatment, even in remitters [6,22,23]. In the present investigation, we found that almost 90% of remitters had at least one residual symptom domain of mild intensity. This is similar to figures reported by Nierenberg et al. [6] and Ioveno et al. [22]. Similar to other studies, the most common residual symptom domain in our patients was anxiety [6,26]. Other studies have reported residual insomnia [23] and sleep disturbances [6,22] to be the most common residual symptoms domains. These differences may be due to the use of different scales and definitions. Development of a consensus on the definition and measurement of residual symptoms would be desirable to enable results between studies to be compared, thus improving understanding.

Interestingly, we found the strongest association between patient functioning and residual core mood symptoms, and we also found a significant interaction with pain and anxiety. The absence of pain increased the chances of normal functioning, regardless of the presence of residual anxiety. However, the absence of residual anxiety increased the chances of normal functioning only if pain was not present. Of note, we found residual insomnia significantly less strongly related to patient functioning than residual core mood symptoms. In addition, no association was found for residual somatic symptoms. It is remarkable that baseline depression severity and previous depression episodes were not significantly related to functional impairment. This further supports the previous finding that residual symptoms are more important than previous episodes of depression in the prognosis of the patient [5].

The different degree of association of each residual symptom with patient functioning might have prognostic implications and requires further investigation. In line with this, several recent studies tried to identify

which specific residual symptoms are predictive of relapse or recurrence [16,26,30,31]. Residual anxiety symptoms were found to be predictive of relapse [26,30,31]. The picture for residual insomnia was less clear, with both positive [16,30] and negative associations reported [6]. Although preliminary, these findings suggest that some residual symptoms present a greater risk for relapse than others.

This study has the following limitations: The primary study from which our data were drawn was not designed to assess residual symptoms, and our results are based on a post-hoc analysis. Our analysis has inherent limitations of post-hoc analysis; measures were those used in the source study. Antidepressant history, before baseline, was not collected, therefore percentage of naïve patients and already treated patients are unknown. This analysis has included a selected population of patients with MDD; patients who had a response to acute antidepressant treatment. This may limit the generalizability of the results to other types of patients not included in this analysis. Our research focused on selected residual symptoms domains and did not include domains such as fatigue or other symptoms not included in the HAMD-17. We also cannot rule out the possibility that a small proportion of the symptoms reported might have been treatment-emergent and not residual.

Conclusions

In summary, our results contribute to a better understanding of the role of specific residual symptoms domains on functional impairment in depression. We found that different residual symptoms have different degrees of association with patient functioning. This indicates that specific residual symptoms domains may be targets for intervention if normal functioning is the treatment objective.

Competing interests

Dr. Irene Romera, Dr. Antonio Ciudad, Pepa Polavieja and Dr. Inmaculada Gilaberte are employees of Eli Lilly. Dr. Irene Romera is also an affiliate with the Universidad Autónoma de Barcelona, Departamento de Psiquiatría. Dr. Victor Perez has received grant support from Eli Lilly, Lundbeck, Boehringer, Pfizer, Astra Zeneca, and GSK; has received honoraria from Servier, Eli Lilly, BMS-Otsuka, GSK, Astra Zeneca, and Boehringer; has served as a consultant for and/or on advisory boards for Eli Lilly, BMS, and AstraZeneca. Dr. Luis Caballero has served on advisory boards for Eli Lilly. Dr. Miguel Roca has received grant support from Almirall, Lundbeck and Janssen and served on advisory boards for Eli Lilly and Wyeth.

Authors' contributions

IR, PP and IG, have been involved in the analysis. All authors have been involved in the interpretation of the data, decision to submit the manuscript for publication and have read and approved the final manuscript. IR has been involved in writing the manuscript.

Acknowledgements

We thank Alistair Reeves for editing assistance, Ígor Martín from Chiltern International Inc. for his support with the statistical analysis, Irene Fregenal from Lilly Spain, Irene Fregenal from Lilly Spain for editing support, the principal investigators, and the patients for their voluntary participation. This study was funded by Eli Lilly and Company.

Author details

[1]Department of Clinical Research Lilly, S.A. Avenida de la Industria 30, 28108, Alcobendas, Spain. [2]Autonomous University of Barcelona, Barcelona, Spain. [3]Department of Psychiatry, Hospital Santa Creu i Sant Pau, Autonomous University of Barcelona / CIBERSAM, Barcelona, Spain. [4]Department of Psychiatry, Hospital Puerta de Hierro, Madrid, Spain. [5]Department of Psychiatry, Joan March Hospital, Rediapp, Palma de Mallorca, Spain.

Received: 23 January 2013 Accepted: 30 January 2013
Published: 11 February 2013

References

1. Romera I, Perez V, Menchón JM, Delgado-Cohen H, Polavieja P, Gilaberte I: **Social and occupational functioning impairment in patients in partial versus complete remission of a major depressive disorder episode. A six-month prospective epidemiological study.** *Eur Psychiatry* 2010, **25:**58–65.
2. Zimmerman M, Posternak MA, Chelminski I: **Heterogeneity among depressed outpatients considered to be in remission.** *Compr Psychiatry* 2007, **48:**113–117.
3. Paykel ES, Ramana R, Cooper Z, Hayhurst H, Kerr J, Barocka A: **Residual symptoms after partial remission: an important outcome in depression.** *Psychol Med* 1995, **25:**1171–1180.
4. Pintor L, Torres X, Navarro V, Matrai S, Gastó C: **Is the type of remission after a major depressive episode an important risk factor to relapses in a 4-year follow up?** *J Affect Disord* 2004, **82:**291–296.
5. Judd LL, Akiskal HS, Maser JD, Zeller PJ, Endicott J, Coryell W, Paulus MP, Kunovac JL, Leon AC, Mueller TI, Rice JA, Keller MB: **Major depressive disorder: a prospective study of residual subthreshold depressive symptoms as predictor of rapid relapse.** *J Affect Disord* 1998, **50:**97–108.
6. Nierenberg AA, Husain MM, Trivedi MH, Fava M, Warden D, Wisniewski SR, Miyahara S, Rush AJ: **Residual symptoms after remission of major depressive disorder with citalopram and risk of relapse: a STAR*D report.** *Psychol Med* 2010, **40:**41–50.
7. Romera I, Pérez V, Menchón JM, Polavieja P, Gilaberte I: **Optimal cutoff point of the Hamilton Rating Scale for Depression according to normal levels of social and occupational functioning.** *Psychiatry Res* 2011, **30:**133–137.
8. Miller IW, Keitner GI, Schatzberg AF, Klein DN, Thase ME, Rush AJ, Markowitz JC, Schlager DS, Kornstein SG, Davis SM, Harrison WM, Keller MB: **The treatment of chronic depression, part 3: psychosocial functioning before and after treatment with sertraline or imipramine.** *J Clin Psychiatry* 1998, **59:**608–619.
9. Keller MB: **Past, present, and future directions for defining optimal treatment outcome in depression: remission and beyond.** *JAMA* 2003, **289:**3152–3160.
10. Ciudad A, Alvarez E, Roca M, Baca E, Caballero L, Garcia De Polavieja P, Casillas M, Valladares A, Gilaberte I: **Early Response and Early Remission as Predictors of Good Outcome of a Depressive Episode.** *J Clin Psychiatry* 2012, **73:**185–191.
11. American Psychiatric Association: *DSM-TR Diagnostic and Statistic Manual of Mental Health Disorders Text Revision, ed. 4*. Washington: American Psychiatric Association; 2000.
12. Hamilton M: **A rating scale for depression.** *J Neurol Neurosurg Psychiatry* 1960, **23:**56–62.
13. Guy W: *1976 ECDEU assessment manual for psychopharmacology*. Rockville, Md. U. S: Dept. of Health, Education, and Welfare, Public Health Service, Alcohol, Drug Abuse, and Mental Health Administration, National Institute of Mental Health, Psychopharmacology Research Branch, Division of Extramural Research Programs; 1976:313–331.
14. Goldman HH, Skodol AE, Lave TR: **Revising axis V for DSM-IV: a review of measures of social functioning.** *Am J Psychiatry* 1992, **149:**1148–1156.
15. Spitzer RL, Gibbon M, Endicott J, Mental Health Status, Functioning and Disability Measures. In Handbook of psychiatric measures: *Global Assessment Scale (GAS), Global Assessment of Functioning (GAF) Scale, Social and Occupational Functioning Assessment Scale (SOFAS)*. Washington DC: American Psychiatric Association: 1st edition. Edited by First MB; 2000:96–100.

16. Dombrovski AY, Cyranowski JM, Mulsant BH, Houck PR, Buysse DJ, Andreescu C, Thase ME, Mallinger AG, Frank E: **Which symptoms predict recurrence of depression in women treated with maintenance interpersonal psychotherapy?** *Depress Anxiety* 2008, **25:**1060–1066.
17. DeLoach LJ, Higgins MS, Caplan AB, Stiff JL: **The visual analog scale in the immediate postoperative period: intrasubject variability and correlation with a numeric scale.** *Anesth Analg* 1998, **86:**102–106.
18. Romera I, Fernández-Pérez S, Montejo AL, Caballero F, Caballero L, Arbesú JÁ, Delgado-Cohen H, Desaiah D, Polavieja P, Gilaberte I: **Generalized anxiety disorder, with or without co-morbid major depressive disorder, in primary care: prevalence of painful somatic symptoms, functioning and health status.** *J Affect Disord* 2010, **127:**160–168.
19. Katz J, Melzack R: **Measurement of pain.** *Surg Clin North Am* 1999, **79:**231–252.
20. Bodian CA, Freedman G, Hossain S, Eisenkraft JB, Beilin Y: **The visual analog scale for pain: clinical significance in postoperative patients.** *Anesthesiology* 2001, **95:**1356–1361.
21. Hosmer DW, Lemeshow S: **Goodness-of-fit test for the multiple logistic regression model.** *Communication in Statistics – Theory and Methods* 1980, **9:**1043–1069.
22. Iovieno N, van Nieuwenhuizen A, Clain A, Baer L, Nierenberg AA: **Residual symptoms after remission of major depressive disorder with fluoxetine and risk of relapse.** *Depress Anxiety* 2011, **28:**137–144.
23. McClintock SM, Husain MM, Wisniewski SR, Nierenberg AA, Stewart JW, Trivedi MH, Cook I, Morris D, Warden D, Rush AJ: **Residual symptoms in depressed outpatients who respond by 50% but do not remit to antidepressant medication.** *J Clin Psychopharmacol* 2011, **31:**180–186.
24. Conradi HJ, Ormel J, de Jonge P: **Presence of individual (residual) symptoms during depressive episodes and periods of remission: a 3-year prospective study.** *Psychol Med* 2011, **8:**1–10.
25. Benvenuti A, Rucci P, Calugi S, Cassano GB, Miniati M, Frank E: **Relationship of residual mood and panic-agoraphobic spectrum phenomenology to quality of life and functional impairment in patients with major depression.** *Int Clin Psychopharmacol* 2010, **25:**68–74.
26. Taylor DJ, Walters HM, Vittengl JR, Krebaum S, Jarrett RB: **Which depressive symptoms remain after response to cognitive therapy of depression and predict relapse and recurrence?** *J Affect Disord* 2010, **123:**181–187.
27. Bertschy G, Haffen E, Gervasoni N, Gex-Fabry M, Osiek C, Marra D, Aubry JM, Bondolfi G: **Self-rated residual symptoms do not predict 1-year recurrence of depression.** *Eur Psychiatry* 2010, **25:**52–57.
28. Roca M, García-Toro M, García-Campayo J, Vives M, Armengol S, García-García M, Asensio D, Gili M: **Clinical differences between early and late remission in depressive patients.** *J Affect Disord* 2011, **134:**235–241. Epub 2011.
29. Ozyüksel B, Uluğ B: **[The association between disability and residual symptoms in depressive patients: a 3-month follow-up.].** *Turk Psikiyatri Derg* 2007, **18:**323–332.
30. Dombrovski AY, Mulsant BH, Houck PR, Mazumdar S, Lenze EJ, Andreescu C, Cyranowski JM, Reynolds CF: **Residual symptoms and recurrence during maintenance treatment of late-life depression.** *J Affect Disord* 2007, **103:**77–82.
31. Yang H, Chuzi S, Sinicropi-Yao L, Johnson D, Chen Y, Clain A, Baer L, McGrath PJ, Stewart JW, Fava M, Papakostas GI: **Type of residual symptom and risk of relapse during the continuation/maintenance phase treatment of major depressive disorder with the selective serotonin reuptake inhibitor fluoxetine.** *Eur Arch Psychiatry Clin Neurosci* 2010, **260:**145–150.

doi:10.1186/1471-244X-13-51
Cite this article as: Romera *et al.*: Residual symptoms and functioning in depression, does the type of residual symptom matter? A post-hoc analysis. *BMC Psychiatry* 2013 **13**:51.

European Psychiatry 27 (2012) e1

Available online at ScienceDirect
www.sciencedirect.com

Elsevier Masson France
EM|consulte
www.em-consulte.com/en

Corrigendum

Corrigendum to "Social and occupational functioning impairment in patients in partial versus complete remission of a major depressive disorder episode. A 6-month prospective epidemiological study". [Eur Psychiatry 2010;25:58–65]

I. Romera [a,*,b], V. Perez [c], J.M. Menchón [d], H. Delgado-Cohen [a,b], P. Polavieja [a,b], I. Gilaberte [a,b]

[a] *Clinical Research Department, Lilly, SA, Avenida de la Industria, 30, 28108 Alcobendas, Madrid, Spain*
[b] *Universidad Autónoma de Barcelona, 08193, Barcelona, Spain*
[c] *Department of Psychiatry, Hospital de Sant Pau i de la Santa Creu, C/Sant Antoni Maria Claret, CIBERSAM, Universidad Autónoma de Barcelona, 167, 08025 Barcelona, Spain*
[d] *Department of Psychiatry, Hospital Universitari de Bellvitge, Feixa Llarga sn, Hospitalet de Llobregat, CIBERSAM, 08907 Barcelona, Spain*

ARTICLE INFO

Article history:
Received 6 October 2008
Received in revised form 30 December 2008
Accepted 19 February 2009
Available online 6 December 2011

The principal author reports that her full affiliation, and a co-author's full affiliation, which includes the Universidad Autónoma de Barcelona, should have appeared as above when the article was originally published in the first issue of 2010.

DOI of original article: 10.1016/j.eurpsy.2009.02.007
* Corresponding author.
E-mail address: romera_irene@lilly.com (I. Romera).

doi:10.1016/j.eurpsy.2011.09.001

Psychiatry Research 198 (2012) 181

Contents lists available at SciVerse ScienceDirect

Psychiatry Research

journal homepage: www.elsevier.com/locate/psychres

Corrigendum

Corrigendum to "Optimal cutoff point of the Hamilton Rating Scale for Depression according to normal levels of social and occupational functioning" [Psychiatry Res. 186 (2011) 133-137]

Irene Romera[a,d,*], Víctor Pérez[b,d,1], José Manuel Menchón[c,2], Pepa Polavieja[a,3], Inmaculada Gilaberte[a,3]

[a] Clinical Research Department, Lilly, S.A., Avenida de la Industria, 30, Alcobendas E-28108, Madrid, Spain
[b] Department of Psychiatry, Hospital de Sant Pau i de la Santa Creu. C/Sant Antoni Maria Claret, 167. E-08025, Barcelona, CIBERSAM, Spain
[c] Department of Psychiatry, Hospital Universitari de Bellvitge. Feixa Llarga, sn. E-08907, Hospitalet de Llobregat, Barcelona, CIBERSAM, Spain
[d] Universidad Autónoma de Barcelona, 08193 Bellaterra, Barcelona, Spain

The authors regret that an affiliation had not been included in the original published version, the missing affiliation, Universidad Autónoma de Barcelona, is now included above.

DOI of original article: http://dx.doi.org/10.1016/j.psychres.2010.06.023.
* Corresponding author. Tel.: +34 91 663 50 00; fax: +34 91 663 52 31.
E-mail addresses: romera_irene@lilly.com (I. Romera), vperez@hsp.santpau.es (V. Pérez), jmenchon@csub.scs.es (J.M. Menchón), polavieja_pepa@lilly.com (P. Polavieja), gilaberte_inmaculada@lilly.com (I. Gilaberte).
[1] Tel.: +34 93 291 90 00.
[2] Tel.: +34 93 260 76 00.
[3] Tel.: +34 91 663 50 00; fax: +34 91 663 52 31.

0165-1781/$ – see front matter
http://dx.doi.org/10.1016/j.psychres.2012.08.018

V-DISCUSIÓN

V-DISCUSIÓN

A raíz de las investigaciones presentadas:

1. La presencia de síntomas residuales, remisión parcial, tras el tratamiento agudo de un episodio de depresión mayor se asocia de forma significativa con una alteración de la funcionalidad social y laboral del paciente, la cual que persiste incluso tras 6 meses de tratamiento de continuación. Del mismo modo, la presencia de síntomas residuales se asocia a un mayor coste de la enfermedad derivado de una mayor ausencia del trabajo por enfermedad.
2. Un punto de corte ≤5 en la escala HAM-D17 se ha mostrado como un mejor predictor de niveles normales de funcionamiento social y ocupacional que otros puntos de corte. Estos datos sugieren que cuando se tiene en cuenta la funcionalidad, un punto de corte menor o igual a 7 podría ser demasiado alto para considerar remisión en el TDM.
3. La contribución de los distintos tipos de síntomas residuales sobre la alteración de la funcionalidad se ha mostrado diferente. De forma que los síntomas residuales nucleares se asociaron a una mayor alteración de la funcionalidad, al igual que la interacción entre los síntomas residuales de ansiedad y el dolor. Sin embargo, otro tipo de síntomas residuales mostraron una menor asociación e incluso, en el caso de los síntomas residuales somáticos, no se encontró una asociación significativa.

Síntomas residuales y pronóstico funcional del paciente

Los datos resultantes de las investigaciones presentadas en esta tesis muestran que la remisión parcial del episodio depresivo se asocia con una importante alteración de la funcionalidad social y laboral del paciente, la cual persiste incluso después de seis meses de tratamiento antidepresivo. De manera global, los pacientes que tras el episodio agudo presentaron síntomas residuales no alcanzaron niveles normales de

funcionamiento al final del estudio, tras seis meses de seguimiento. Por el contrario, los pacientes en remisión completa mantuvieron niveles normales de funcionamiento durante todo el estudio. De hecho, el estar en remisión completa tras el periodo agudo, estuvo fuertemente asociado con alcanzar a medio plazo un funcionamiento social y laboral normal. De forma que, estos pacientes tuvieron tres veces más probabilidad de alcanzar una funcionalidad normal al final del estudio en relación con aquellos pacientes en remisión parcial. Nuestros resultados subrayan la importancia de tratar el paciente hasta lograr la remisión completa del episodio de depresión, no sólo para lograr un estado asintomático, sino también para poder mejorar el pronóstico funcional del paciente.

Merece la pena mencionar la escasez de estudios que evalúen los aspectos funcionales de la depresión y más específicamente, que valoren el impacto de la remisión parcial, presencia de síntomas residuales, en el pronóstico funcional del paciente. De hecho, el Estudio I presentado en esta tesis el primer estudio prospectivo realizado en España que aborda este aspecto y de los pocos publicados hasta la fecha. En este sentido, nuestros resultados son consistentes con el estudio realizado por Kennedy y colaboradores en sesenta pacientes con depresión. A partir de un episodio índice de depresión, los pacientes que remitieron con síntomas residuales o por debajo de la sintomatología residual, fueron seguidos a los 8-10 años. Los pacientes que remitieron con síntomas residuales mostraron mayor deterioro de la funcionalidad, según la SAS (Social Adjusment Scale), longitudinalmente y al final del periodo de evaluación (Kennedy *et al.,* 2004).

Los resultados del análisis de regresión logística de nuestro estudio mostraron que el factor más fuertemente asociado con lograr el funcionamiento normal en el momento final fue estar en remisión completa, ausencia de síntomas residuales, basalmente.

Esto contrasta con el hecho de que el número de episodios previos no se encontró asociado a una buena funcionalidad al final del estudio. Sin embargo, estos resultados serían consistentes con estudios anteriores que han mostrado que la presencia de síntomas residuales es un predictor más importante de recaída que el número de episodios depresivos previos (Judd *et al.,* 1998; Pintor *et al.,* 2004).

Otro factor asociado a alcanzar niveles normales de funcionamiento fue la mejoría sintomática, reducción en la puntuación de la HAMD-17, a lo largo del estudio. Esto es consistente con la alta correlación encontrada entre la escala SOFAS y la HAMD-17, indicando correlación entre la mejoría sintomática y funcional. A este respecto, aunque los pacientes en remisión parcial mostraron mejoras en la sintomatología a lo largo del período de seis meses de seguimiento, globalmente no alcanzaron un funcionamiento normal al final del estudio. Esto podría ser en parte explicado por un posible retraso entre la recuperación sintomática y la recuperación funcional (Furukawa *et al.,* 2001). En este estudio, Furukawa *et al.* (2001) encontró que la recuperación funcional no se producía hasta pasados unos meses de remisión sintomática. Sin embargo, esto contrasta con los datos más recientes de Ciudad *et al.* (2012) donde aquellos pacientes que remitían tempranamente, en las seis primeras semanas de tratamiento agudo, alcanzaban niveles normales de funcionalidad tan pronto como a las seis semanas de tratamiento, no pareciendo existir un retraso entre la mejoría sintomática y la mejoría funcional. Por lo tanto, los datos de Ciudad *et al.* (2012) hacen pensar que para favorecer la recuperación funcional no solamente se precisa una recuperación del episodio sin síntomas residuales, sino que esta recuperación sea temprana.

Cabe destacar que aunque la mayoría de pacientes en remisión parcial no tenían niveles normales funcionales, sólo en un tercio se cambió la estrategia terapéutica antidepresiva durante los seis meses de seguimiento. Cifra ligeramente superior a la observada en el grupo de pacientes en remisión completa. Este hallazgo sugiere que,

si bien la resolución de la sintomatología sin síntomas residuales y la recuperación funcional, debe ser el objetivo del tratamiento, no parece evidenciarse una actitud activa al respecto. Este dato es relevante ya que la ausencia de un tratamiento adecuado o la falta de optimización del mismo es uno de los factores que puede estar asociado con la persistencia del deterioro psicosocial en la depresión (Kennedy *et al.,* 2007; Papakostas et al., 2009). En este sentido, la búsqueda individualizada del tratamiento o estrategias terapéuticas adecuadas para cada paciente, de forma activa o dinámica, es decir evitando una actitud de "esperar y ver", no dilatando en el tiempo la toma de decisiones terapéuticas, puede favorecer la consecución de los resultados clínicos de remisión y recuperación funcional (Romera *et al.,* 2012a; Romera *et al.*, 2012b).

En relación con la funcionalidad laboral y bajas por enfermedad, más de la mitad de los pacientes, con trabajo remunerado, en remisión parcial estuvieron de baja por enfermedad en comparación con menos de una tercera parte de los pacientes en remisión completa. Asimismo, estuvieron de media, tres veces más días de baja por enfermedad. Esto se traduce en un aumento significativo en los costes indirectos debido a las bajas por enfermedad asociado a la remisión parcial. Este hallazgo es consistente con un estudio previo realizado en Suecia (Soboki *et al.,* 2006). Sin embrago, cabría señalar, que el absentismo laboral puede ser impulsado por muchas causas distintas a la depresión y que a veces es difícil atribuirlo a una única causa.

En nuestro estudio no se encontraron asociaciones significativas entre la historia de trastornos de la personalidad o trastorno distímico y recuperación funcional al final del estudio, sin embargo estos factores que hay que tenerlos en cuenta como posibles barreras para lograr la recuperación del paciente (Kennedy *et al*., 2007).

Punto de corte en la HAMD-17 que mejor predice una funcionalidad normal

De acuerdo con el análisis de 292 pacientes con trastorno depresivo mayor, para encontrar el punto de corte óptimo de la escala HAMD-17 que mejor predice niveles normales de funcionamiento social y ocupacional, una puntuación ≤ 5 maximizó la sensibilidad y especificidad, en comparación con otras puntuaciones. Por lo tanto, cuando se tiene en cuenta no sólo los síntomas, sino también la recuperación de la función social y laboral, el punto de corte tradicional de la HAMD-17 podría considerarse demasiado alto. Es decir, una puntuación HAMD-17 ≤ 7 no implicaría tener necesariamente niveles normales de funcionalidad.

Estos resultado, por tanto, apoyan la idea de que si se considera el funcionamiento, un punto de corte de 7 en la escala HAMD-17 podría ser demasiado alto, según lo sugerido por otros investigadores (Riso *et al.,* 1997; Zimmerman *et al.,* 2005, 2006b, 2007, 2012a). Zimmerman et al. (2005) encontraron que los pacientes que obtuvieron una puntuación inferior o igual a 2 mostraron significativamente menor deterioro psicosocial y una mejor calidad de vida en comparación con los pacientes con puntuaciones de 3 a 7. Este mismo autor, en un estudio reciente realizado en 274 pacientes con depresión en remisión (HAMD-17 ≤7), encontró resultados similares (Zimmerman *et al*., 2012a). Los pacientes con puntuaciones 0-2 en la HAMD-17 tenían niveles significativamente mejores de funcionamiento psicosocial, calidad de vida y una mayor satisfacción con su salud mental, en comparación con pacientes con puntuaciones de 3-7 (Zimmerman et al., 2012a). Riso *et al.* (1997) encontraron que una puntuación ≤ 6 predecía menor número de actitudes disfuncionales y mejor funcionamiento global, comparado con una puntuación de 7 a 10. Resultados similares se han encontrado con la escala de depresión de Montgomery-Asberg, donde los pacientes con puntuaciones más bajas (≤ 4 frente a 5-9) tuvieron un mejor funcionamiento global (Zimmerman *et al.,* 2004). Por último, y más específicamente,

un punto de corte ≤ 5 en la HAMD-17 está de acuerdo con las recomendaciones del ACNP que sugieren el uso de puntos de corte ≤ 5 (Rush *et al.,* 2006).

En acuerdo con los resultados sobre el punto de corte que mejor predice una funcionalidad normal, hemos encontrado que el 24% de los pacientes con un HAMD-17 ≤ 7 no tiene niveles normales de funcionamiento. Así, un porcentaje importante de pacientes que se considera que se han recuperado del episodio de TDM, en base a la definición de remisión en la práctica clínica, seguiría padeciendo la enfermedad. Es decir, una puntuación HAMD ≤ 7 no implica necesariamente tener niveles normales de funcionalidad. Estos resultados en parte son consistentes con un estudio reciente de Zimmerman *et al.* (2012), donde aproximadamente la mitad de los pacientes con puntuaciones por debajo de 7 en la HAMD-17 no se consideran en remisión. Estos pacientes, que no se consideran en remisión, tenían niveles significativamente peores de funcionalidad laboral, familiar, social y global que los pacientes que se consideraban en remisión (Zimmerman *et al.,* 2012b). Nuestros datos también son consistentes con un análisis derivado del estudio STAR-D, donde se observó que un 19.5% de los pacientes que alcanzaron remisión (QIDS-SR<5) tras 12 semanas de tratamiento presentaban una funcionalidad alterada (Work and Social Adjustment Scale ≥ 10) (Cohen *et al.,* 2013).

El hecho de que haya un grupo de pacientes en remisión que presente alteración funcional podría ser debido, como hemos comentado anteriormente, a que los síntomas tienden a mejorar considerablemente antes que la funcionalidad, y que la recuperación funcional está por detrás de la recuperación clínica (Furukawa *et al.,* 2001). Por lo tanto, si nuestro estudio hubiese durado más de 6 meses, el porcentaje de pacientes en remisión, pero aún sufriendo deterioro funcional, podría haber sido menor. Otros factores que pueden estar asociados son la presencia de co-morbilidad

médica o psiquiátrica y un bajo nivel pre-mórbido de funcionamiento (Kennedy *et al.,* 2007).

Un aspecto que merece la pena mencionar, es que la remisión, según el HAMD-17, es un constructo unidimensional, incluye únicamente aspectos sintomáticos. Según Zimmerman *et al.* (2011; 2012b), la remisión debería ser un constructo más amplio, que incluya no sólo aspectos sintomáticos sino también otros indicadores del estado clínico como la funcionalidad, la calidad de vida, la capacidad de afrontamiento al estrés, así como la sensación general de bienestar (Zimmerman *et al.,* 2011; Zimmerman et al., 2012b). Esta conceptualización multidimensional de la depresión es también un área de reciente interés por el Instituto Nacional de Salud Mental de Estados Unidos (National Institute of Mental Health, NIMH) (Cohen *et al.,* 2013). En este sentido, han valorado como una evaluación multidimensional (Individual Burden of Illness Index for Depression, IBI-D), que incluye aspectos sintomáticos, funcionales y de la calidad de vida, capta adecuadamente la carga completa de la depresión antes y después de tratamiento, ofreciendo una medida más precisa de recuperación (Cohen *et al.,* 2013).

Los resultados de nuestro análisis sobre el punto de corte de la HAMD-17 que mejor predice una buena funcionalidad indican que, entre los pacientes con puntuaciones menores o iguales a 7, existe cierta heterogeneidad en cuanto al nivel de funcionalidad. La implicación práctica clínica de nuestros hallazgos es la importancia de medir, en el seguimiento de los pacientes que sufren depresión, no sólo la mejoría clínica, sino también la mejoría funcional. Esto es así porque la remisión implica tanto la ausencia de síntomas como de deterioro funcional. Este enfoque está de acuerdo al defendido por el DSM-IV, que sugiere que los síntomas de la depresión mayor deben ser evaluados en términos de su impacto funcional en el área social, ocupacional, u

otro tipo de área relevante, y recomienda el uso de una evaluación global de la funcionalidad (Goldman,1992). Sin embargo, podría ser un reto dado que el uso de escalas funcionales, tales como la SOFAS o la SDS, es poco común en la práctica clínica habitual. La existencia nuevas escalas de reciente aparición, como la RDQ (Remission from Depression Questionnaire), sencillas de aplicar, aceptadas por el paciente, que incluyan aspectos sintomáticos así como funcionales, pueden ser estrategias a tener en cuenta para la mejora del proceso de evaluación clínica del paciente (Zimmerman *et al.,* 2011).

A raíz de nuestros resultados, si tenemos en cuenta la funcionalidad, podría sugerirse como posible solución disminuir el punto de corte de la HAMD-17 para determinar remisión. Sin embargo, es importante considerar el valor pronóstico que ha demostrado el punto de corte tradicional de la HAMD-17 derivado de numerosos estudios clínicos. Por el contrario, ningún estudio ha demostrado que un corte inferior de 7 en la HAMD-17 sea un indicador pronóstico más válido. Por lo tanto, sería necesario estudios adicionales del valor pronóstico, como la capacidad de predicción de recaídas, de puntos de corte más bajos.

Tipo de síntomas residual y alteración de la funcionalidad

En cuanto la relación entre distintos síntomas residuales (nucleares, insomnio, ansiedad, somáticos) y la alteración funcionalidad, encontramos que estos síntomas impactan de manera diferente sobre la funcionalidad del paciente. De forma los síntomas nucleares residuales se asocian de una manera más marcada, al igual que la interacción entre el dolor y los síntomas residuales de ansiedad. Sin embargo, los síntomas residuales de insomnio se encontraron menos fuertemente relacionados con el funcionamiento del paciente y no se mostró asociación para los síntomas somáticos residuales.

A nuestro entender, este es el primer estudio que investiga el papel de determinados síntomas residuales del TDM sobre el funcionamiento del paciente. La mayoría de las publicaciones acerca de síntomas residuales se enfocan en su descripción y su relación con las recaídas y recurrencias de la depresión (Iovieno *et al.,* 2011; McClintock *et al.,* 2011; Conradi *et al.,* 2011; Taylor *et al.,* 2010; Bertschy *et al.,* 2010; Nierenberg *et al*., 2010). Publicaciones más recientes han evaluado su relación con el tiempo hasta la remisión (Roca *et al.,* 2011; Nierenberg *et al*., 2010). Pocos estudios han investigado específicamente la relación entre los síntomas residuales y el deterioro funcional, y se han centrado en el impacto global de estos síntomas en el funcionamiento (Romera *et al*., 2010; Miller *et al.,* 1998; Ozyüksel *et al.,* 2007), sin por tanto, analizar específicamente la contribución de cada tipo de síntoma residual.

El diferente grado de asociación de cada síntoma residual con el funcionamiento del paciente podría tener implicaciones en el pronóstico de la enfermedad y requiere ser investigado. En esta línea, varios estudios recientes han tratado de identificar los síntomas residuales específicos que son predictivos de recaída o de recurrencia (Taylor *et al.* 2010; Dombrovski *et al*., 2007; Dombrovski *et al.,* 2008; Yang *et al.,* 2010). Si bien se ha encontrado que los síntomas residuales de ansiedad fueron factores predictivos de recaída (Taylor *et al.,* 2010; Dombrovski *et al.,* 2007; Yang *et al.,* 2010), el panorama para el insomnio residual fue menos claro, con asociaciones positivas (Dombrovski *et al.,* 2007; Dombrovski *et al.,* 2008) y negativas comunicadas (Nierenberg *et al.,* 2010). Estos hallazgos, aunque preliminares, sugieren que algunos de los síntomas residuales presentan un mayor riesgo de recaída que otros. Nuestros resultados indican que determinados dominios de síntomas residuales podrían ser objeto de intervención con el fin de perseguir la restauración del funcionamiento del paciente.

Es de destacar que la gravedad inicial de la depresión y la presencia de episodios previos de depresión, no se relacionaron significativamente con el deterioro funcional del paciente. Esto refuerza hallazgos previos donde los síntomas residuales se encontraron más relacionados con el pronóstico del paciente que los episodios anteriores de depresión (Judd *et al.,* 1998).

Al igual que mostraron otros autores, nuestro análisis de síntomas residuales tras el tratamiento agudo ha evidenciado que son una entidad muy frecuente (Iovieno *et al.,* 2011; McClintock *et al.,* 2011; Nierenberg *et al.,* 2010). Como en otros estudios, el dominio sintomático residual más frecuente en nuestros pacientes fue la ansiedad (Taylor *et al*., 2010; Nierenberg *et al*., 2010). Sin embargo, otros autores han reportado el insomnio residual (McClintock *et al*., 2011) y los trastornos del sueño (Iovieno *et al*., 2011; Nierenberg *et al*., 2010) como los dominios de síntomas residuales más comunes. Estas diferencias en cuanto a la frecuencia pueden ser debidas a la variabilidad entre los estudios en la utilización de escalas y definiciones. Por tanto, la presencia de un consenso sobre la definición y medición de los síntomas residuales en el paciente con depresión, así como la existencia de escalas específicas para su valoración, sería deseable para permitir una mejor comprensión de estos síntomas.

Limitaciones

Estudio I

En primer lugar, en relación con un diseño epidemiológico, de seguimiento de dos cohortes, de manera abierta y naturalista, no se puede descartar los sesgos inherentes a este tipo de estudios, que pueden tener un efecto sobre la recogida de datos. A pesar de estas limitaciones, gracias al diseño naturalista, los pacientes reflejan en mejor medida la realidad de la práctica clínica. La segunda limitación es referente al momento de inclusión de los pacientes. Los pacientes estaban en remisión parcial o en remisión completa y se trataron previamente durante 12 semanas; es decir, los

pacientes se incluyeron en el estudio durante el curso del episodio de TDM y no en la fase aguda del episodio. Por lo tanto, esto podría haber disminuido la precisión del diagnóstico de trastorno depresivo mayor. Sin embargo, con el fin de minimizar este posible sesgo, los pacientes tenían que tener una historia de al menos un episodio de depresión anterior y el diagnóstico de trastorno depresivo mayor fue realizado por el investigador, en base a criterios DSM-IV, quien también era el psiquiatra que trataba al paciente. La tercera limitación hace referencia a que la recuperación funcional se sitúa en el corto-medio plazo y no proporciona datos a largo plazo de asociación entre la remisión parcial, con síntomas residuales, y el funcionamiento del paciente. Por último, hay que tener en cuenta que el análisis de la sensibilidad y la especificidad de la HAMD-17, como indicador de niveles normales de funcionalidad, se centró en un punto específico del tiempo, seis meses después de la consecución de la remisión.

Estudio II

En primer lugar, al igual que en el estudio I, no se puede descartar los sesgos inherentes a un estudio abierto que pueden tener un efecto sobre la recogida de datos. Segundo, el estudio de los tipos de síntomas residuales y su asociación con la alteración funcional, se centró en determinados dominios de síntomas residuales derivados de la HAMD-17. Esta es una limitación común a otros estudios de valoración de los síntomas residuales debido a la carencia de estandarización sobre la evaluación de los mismos. Por último, tampoco podemos descartar la posibilidad de que una pequeña proporción de los síntomas comunicados como residuales podrían haberse derivado del tratamiento, como efectos secundarios.

VI- CONCLUSIONES

VI- CONCLUSIONES

A raíz de los resultados de las investigaciones presentadas podemos concluir que:

La presencia de síntomas residuales, remisión parcial, tras el tratamiento agudo de un episodio de depresión mayor se asocia de forma significativa con una alteración de la funcionalidad social y laboral del paciente, la cual que persiste incluso tras 6 meses de tratamiento de continuación.

La presencia de síntomas residuales se asocia a un mayor coste de la enfermedad derivado de una mayor ausencia del trabajo por enfermedad.

Un punto de corte ≤5 en la escala HAM-D17 se ha mostrado como un mejor predictor de niveles normales de funcionamiento social y ocupacional que otros puntos de corte.

La contribución de los distintos tipos de síntomas residuales sobre la alteración de la funcionalidad se ha mostrado diferente.

Los síntomas residuales nucleares se asociaron a una mayor alteración de la funcionalidad, al igual que la interacción entre los síntomas residuales de ansiedad y el dolor.

Síntomas residuales como los de insomnio mostraron una menor asociación e incluso, en el caso de los síntomas residuales somáticos, no se encontró una asociación significativa.

Estos resultados ponen de manifiesto la importancia de perseguir la remisión del episodio, evitando la persistencia de síntomas residuales, con el fin de mejorar el

pronóstico funcional del paciente. Asimismo, un punto de corte menor o igual a 7 en la HAMD-17 podría asociarse a alteración funcional, lo que implicaría la necesidad de valorar adicionalmente la mejoría funcional, para así conocer de manera más completa y precisa el estado clínico del paciente. Por último, determinados dominios de síntomas residuales podrían ser objeto de intervención con el fin de perseguir la restauración de la funcionalidad del paciente.

En su conjunto, nuestros resultados contribuyen a un mayor conocimiento del rol de los síntomas residuales y la remisión sobre el pronóstico funcional del paciente con depresión. Asimismo, ponen de manifiesto el distinto papel que juegan diferentes dominios de síntomas residuales sobre la alteración funcional. Profundizan sobre la relación existente entre la remisión sintomática y funcional. De forma que nuestros hallazgos, si bien contribuyen a facilitar el abordaje del TDM y la consecución de los objetivos terapéuticos, también ponen de manifiesto nuevos retos futuros.

VII- BIBLIOGRAFÍA

VII- BIBLIOGRAFIA

1. American Psychiatric Association: Practice guideline for the treatment of patients with major depressive disorder, third edition. Available at http://www.psychiatryonline.com/pracGuide/pracGuideChapToc_7.aspx

2. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. Fourth edition. Text revision (DSM-IV®-TR). American Psychiatric Association, 2000, Washington, DC.

3. American Psychiatric Association (2005). Handbook of psychiatric measures, Chapter 8, Mental Health Status, Functioning and Disability Measures. Washington.

4. Alonso, J., Angermeyer, M.C., Bernert, S., Bruffaerts, R., Brugha, T.S., Bryson, H., de Girolamo, G., Graaf, R., Demyttenaere, K., Gasquet, I., Haro, J.M., Katz, S.J., Kessler, R.C., Kovess, V., Lépine, J.P., Ormel, J., Polidori, G., Russo, L.J., Vilagut, G., Almansa, J., Arbabzadeh-Bouchez, S., Autonell, J., Bernal, M., Buist-Bouwman, M.A., Codony, M., Domingo-Salvany, A., Ferrer, M., Joo, S.S., Martínez-Alonso, M., Matschinger, H., Mazzi, F., Morgan, Z., Morosini, P., Palacín, C., Romera, B., Taub, N., Vollebergh, W.A., ESEMeD/MHEDEA 2000 Investigators, European Study of the Epidemiology of Mental Disorders (ESEMeD) Project., 2004. Prevalence of mental disorders in Europe: results from the European Study of the Epidemiology of Mental Disorders (ESEMeD) project. Acta Psychiatrica Scandinavica Suppl 420, 21-27.

5. Bech, P., Allerup, P., Gram, L.F., Reisby, N., Rosenberg, R., Jacobsen, O., Nagy, A., 1981. The Hamilton depression scale. Evaluation of objectivity using logistic models. Acta Psychiatrica Scandinavica 63, 290-299.

6. Bair, M.J., Robinson, R.L., Katon, W., Kroenke, K., 2003. Depression and pain comorbidity: a literature review. Archives of Internal Medicine 163, 2433-2445.

7. Bertschy, G., Haffen, E., Gervasoni, N., Gex-Fabry, M., Osie, C., Marra, D., Aubry, J.M., Bondolfi, G., 2010. Self-rated residual symptoms do not predict 1-year recurrence of depression. European Psychiatry 25, 52-57.

8. Blair-West, G.W., Cantor, C.H., Mellsop, G.W., Eyeson-Annan, M.L., 1999. Lifetime suicide risk in major depression: sex and age determinants. Journal of Affective Disorders 55,171–178

9. Bosc, M., Dubini, A., Polin, V., 1997. Development and validation of a social functioning scale: The Social Adapatation Self-evaluation Scale. European Neuropsychopharmacology 7 suppl. 1: S57-70; discussion S1-3

10. Campayo, A., de Jonge, P., Roy, J.F., Saz, P., de la Cámara, C., Quintanilla, M.A., Marcos, G., Santabárbara, J., Lobo, A., 2010. ZARADEMP Project. Depressive disorder and incident diabetes mellitus: the effect of characteristics of depression. American Journal of Psychiatry 167, 580-588.

11. Ciudad, A., Álvarez, E., Roca, M., Baca, E., Caballero, L., García de Polavieja, P., Casillas, M., Valladares, A., Gilaberte, I., 2012. Early Response and

Early Remission as Predictors of Good Outcome of a Depressive Episode. Journal of Clinical Psychiatry 73, 185-191.

12. Chisholm, D., Diehr, P., Knapp, M., Patrick, D., Treglia, M., Simon, G., 2003. Depression status, medical comorbidity and resource costs. Evidence from an international study of major depression in primary care (LIDO). British Journal of Psychiatry 183, 121-123.

13. Cohen, R.M., Greenberg, J.M., Ishak, W.W., 2013. Incorporating Multidimensional Patient-Reported Outcomes of Symptom Severity, Functioning, and Quality of Life in the Individual Burden of Illness Index for Depression to Measure Treatment Impact and Recovery in MDD. JAMA Psychiatry 70, 343-350

14. Conradi, H.J., Ormel, J., de Jonge, P., 2010. Presence of individual (residual) symptoms during depressive episodes and periods of remission: a 3-year prospective study. Psychological Medicine 8, 1-10.

15. Dombrovski, A.Y., Cyranowski, J.M., Mulsant, B.H., Houck, P.R., Buysse, D.J., Andreescu, C., Thase, M.E., Mallinger, A.G., Frank, E., 2008. Which symptoms predict recurrence of depression in women treated with maintenance interpersonal psychotherapy? Depression and Anxiety 25, 1060-1066.

16. Dumais, A., Lesage, A.D., Alda, M., Rouleau, G., Dumont, M., Chawky, N., Roy, M., Mann, J.J., Benkelfat, C., Turecki, G., 2005. Risk factors for suicide completion in major depression: a case-control study of impulsive and aggressive behaviors in men. American Journal of Psychiatry 162, 2116-2124.

17. Endicott, J., Dorries, KM., 2009. Functional outcomes in MDD: Established and emerging assessment tools. American Journal of Managed Care 15, S328-S334

18. Egede, L.E., 2007. Major depression in individuals with chronic medical disorders: prevalence, correlates and association with health resource utilization, lost productivity and functional disability. General Hospital Psychiatry 29, 409-416.

19. Frank, E., Prien, R.F., Jarrett, R.B., Keller, M.B., Kupfer, D.J., Lavori, P.W., Rush, A.J., Weissman, M.M., 1991. Conceptualization and rationale for consensus definitions of terms in major depressive disorder. Remission, recovery, relapse, and recurrence. Archives of General Psychiatry 48, 851-855.

20. Furukawa, T.A., Takeuchi, H., Hiroe, T., Masiko, H., Kamei, K., Kitamura, T., Takahashi, K., 2001. Symptomatic recovery and social functioning in major depression. Acta Psychiatrica Scandinavica 103, 257–261.

21. Gabilondo, A., Rojas-Farreras, S., Vilagut, G., Haro, J.M., Fernández, A., Pinto-Meza, A., Alonso, J., 2010. Epidemiology of major depressive episode in a southern European country: results from the ESEMeD-Spain project. Journal of Affective Disorders 120, 76-85.

22. García-Campayo, J., Ayuso-Mateos, J.L., Caballero, L., Romera, I., Aragonés, E., Rodríguez-Artalejo, F., Quail, D., Gilaberte, I., 2008. Relationship of Somatic Symptoms With Depression Severity, Quality of Life, and Health Resources Utilization in Patients With Major Depressive Disorder Seeking Primary Health Care in Spain. Primary Care Companion to the Journal of Clinical Psychiatry 10, 355-362.

23. Glassman, A.H., Bigger, J.T. Jr., Gaffney, M., 2009. Psychiatric characteristics associated with long-term mortality among 361 patients having an acute coronary syndrome and major depression: seven-year follow-up of SADHART participants. Archives of General Psychiatry 66, 1022-1029.

24. Goldman, H.H., Skodol, A.E., Lave, T.R., 1992. Revising axis V for DSM-IV: a review of measures of social functioning. American Journal of Psychiatry 149, 1148-56.

25. Greer, T.L., Kurian, B.T., Trivedi, M.H., 2010. Defining and measuring functional recovery from depression. CNS Drugs 24, 267-284.

26. Guze, S.B., Robins, E., 1970. Suicide and primary affective disorders. British Journal of Psychiatry 117, 437–438

27. Hamilton, M., 1960. A rating scale for depression. Journal of Neurology, Neurosurgery and Psychiatry 23, 56-62.

28. Hemingway, H., Marmot, M., 1999. Evidence based cardiology: psychosocial factors in the aetiology and prognosis of coronary heart disease. Systematic review of prospective cohort studies. British Medical Journal 318, 1460-1467.

29. Hirschfeld, R.M., Montgomery, S.A., Keller, M.B., Kasper, S., Schatzberg, A.F., Möller, H.J., Healy, D., Baldwin, D., Humble, M., Versiani, M., Montenegro, R., Bourgeois, M., 2000. Social functioning in depression: a review. Journal of Clinical Psychiatry 61, 268-275.

30. Iglesias, C., Alonso, M., 2009. Residual symptoms in depression. Actas Españolas de Psiquiatria 37, 101-105.

31. Iovieno, N., van Nieuwenhuizen, A., Clain, A., Baer, L., Nierenberg, A.A., 2011. Residual symptoms after remission of major depressive disorder with fluoxetine and risk of relapse. Depression and Anxiety 28, 137-144.

32. Judd, L.L., Akiskal, H.S., Maser, J.D., Zeller, P.J., Endicott, J., Coryell, W., Paulus, M.P., Kunovac, J.L., Leon, A.C., Mueller, T.I., Rice, J.A., Keller, M.B., 1998. Major depressive disorder: A prospective study of residual subthreshold depressive symptoms as predictor of rapid relapse. Journal of Affective Disorders 50, 97-108.

33. Judd, L.L., Akiskal, H.S., Maser, J.D., Zeller, P.J., Endicott, J., Coryell, W., Paulus, M.P., Kunovac, J.L., Leon, A.C., Mueller, T.I., Rice, J.A., Keller, M.B., 1998. A prospective 12-year study of subsyndromal and syndromal depressive symptoms in unipolar major depressive disorders. Archives of General Psychiatry 55, 694–700.

34. Judd, L.L., Paulus, M.J., Schettler, P.J., Akiskal, H.S., Endicott, J., Leon, A.C., Maser, J.D., Mueller, T., Solomon, D.A., Keller, M.B., 2000. Does incomplete recovery from first lifetime major depressive episode herald a chronic course of illness? American Journal of Psychiatry 157, 1501–1504.

35. Keller, M.B., 2003. Past, present, and future directions for defining optimal treatment outcome in depression: remission and beyond. JAMA 289, 3152-3160.

36. Kennedy, N., Paykel, E.S., 2004. Residual symptoms at remission from depression: impact on long-term outcome. Journal of Affective Disorders 80, 135-144.

37. Kennedy, N., Abbott, R., Paykel, E.S., 2004. Longitudinal syndromal and sub-syndromal symptoms after severe depression: 10-year follow-up study. British Journal of Psychiatry 184, 330–336.

38. Kennedy, N., Foy, K., 2005. The Impact of Residual Symptoms on Outcome of Major Depression. Current Psychiatry Reports 7, 441–446

39. Kennedy, N., Foy, K., Sherazi, R., McDonough, M., McKeon, P., 2007. Long-term social functioning after depression treated by psychiatrists: a review. Bipolar Disorders 9, 25-37.

40. Kessler, R.C., Greenberg, P.E., Mickelson, K.D., Meneades, L.M., Wang, P.S., 2001. The effects of chronic medical conditions on work loss and work cutback. Journal of Occupational and Environmental Medicine 43, 218-225.

41. Kessler, R.C., Berglund, P., Demler, O., Jin, R., Koretz, D., Merikangas, K.R., Rush, A.J., Walters, E.E., Wang, P.S., 2003. The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). JAMA 289, 3095-3105.

42. Kroenke, K., Spitzer, R.L., Williams, J.B., 2001. The PHQ-9: validity of a brief depression severity measure. Journal General Internal Medicine 16, 606-613

43. Kuper, H., Marmot, M., Hemingway, H., 2002. Systematic review of prospective cohort studies of psychosocial factors in the etiology and prognosis of coronary heart disease. Seminars in Vascular Medicine 2, 267-314.

44. Kupfer, D.J., 1991. Long-term treatment of depression. Journal of Clinical Psychiatry 52, S28-S34.

45. Kupfer, D.J., Frank, E., Phillips, M.L., 2012. Major depressive disorder: new clinical, neurobiological, and treatment perspectives. Lancet 379, 1045-1055.

46. Leon, A.C., Solomon, D.A., Mueller, T.I., Turvey, C.L., Endicott, J., Keller, B., 1999. The range of impaired functioning tool (LIFERIFT). Psychological Medicine 29, 869–878.

47. Lepine, J.P., Gastpar, M., Mendlewicz, J., Tylee, A., 1997. Depression in the community: the first pan-European study DEPRES (Depression Research in European Society). International Clinical Psychopharmacology 12, 19-29.

48. Lespérance, F., Frasure-Smith, N., Talajic, M., Bourassa, M.G., 2002. Five-Year Risk of Cardiac Mortality in Relation to Initial Severity and One-Year Changes in Depression Symptoms After Myocardial Infarction. Circulation 105, 1049-1053

49. Mathers, C.D., Loncar, D., 2006. Projections of global mortality and burden of disease from 2002 to 2030. PLoS Med 3, e442.

50. McClintock, S.M., Husain, M.M., Wisniewski, S.R., Nierenberg, A.A., Stewart, J.W., Trivedi, M.H., Cook, I., Morris, D., Warden, D., Rush, A.J., 2011. Residual symptoms in depressed outpatients who respond by 50% but do not remit to antidepressant medication. Journal of Clinical Psychopharmacology 31, 180-186.

51. McIntyre, R., Kennedy, S., Bagby, R.M., Bakish, D., 2002. Assessing full remission. Journal of Psychiatry and Neuroscience 27, 235-239

52. Mezuk, B., Eaton, W.W., Albrecht, S., Golden, S.H., 2008. Depression and type 2 diabetes over the lifespan: a meta-analysis. Diabetes Care 31, 2383-2390.

53. Miller, I.W., Keitner, G.I., Schatzberg, A.F., Klein, D.N.., Thase, M.E., Rush, A.J., Marckovitz, J.C., Schlarger, D.S., Kornstein, S., Davis, S.M., Harrison, W.M., Keller, M.B., 1998. The treatment of chronic depression, part 3: psychological functioning before and after treatment with sertraline or imipramine. Journal of Clinical Psychiatry 59, 608-619

54. Mojtabai, R., 2001. Residual Symptoms and Impairment in Major Depression in the Community. American Journal of Psychiatry 158, 1645–1651

55. Möller, H.J., 2008. Outcomes in major depressive disorder: the evolving concept of remission and its implications for treatment. World Journal of Biological Psychiatry 9, 102-114.

56. Moussavi, S., Chatterji, S., Verdes, E., Tandon, A., Patel, V., Ustun, B., 2007. Depression, chronic diseases, and decrements in health: results from the World Health Surveys. Lancet 370, 851-858.

57. National Institute for Health and Clinical Excellence. Depression in adults with a chronic physical health problem. Treatment and management. October 2009

58. National Institute of Healthy and Clinical Excellence: The Treatment and Management of Depression in Adults, in The British Psychological Society & The Royal College of Psychiatrists, 2010. Available from: http://www.nice.org.uk/nicemedia/live/12329/45896/45896.pdf

59. Nierenberg, A.A., Husain, M.M., Trivedi, M.H., Fava., M., Warden, D., Wisniewski, S.R., Miyahara, S., Rush, A.J., 2009. Residual symptoms after remission of major depressive disorder with citalopram and risk of relapse: a STAR*D report. Psychological Medicine 40, 41-50.

60. OMS. Décima Revisión de la Clasificación Internacional de Enfermedades. CIE-10. Trastornos mentales y del comportamiento. Madrid: Meditor 1992.

61. Ormel, J., VonKorf,f M., Ustun, T.B., Pini, S., Korten, A., Oldehinkel, T., 1994. Common mental disorders and disability across cultures. Results from the WHO Collaborative Study on Psychological Problems in General Health Care. JAMA 272, 1741-1748.

62. Ormel, J., Oldehinkel, A.J., Nolen, W.A., Vollebergh, W., 2004. Psychosocial disability before, during, and after a major depressive episode: a 3-wave population-based study of state, scar, and trait effects. Archives of General Psychiatry 61, 387-392.

63. Papakostas, G.I., Petersen, T., Denninger, J.W., Tossani, E., Pava, J.A., Alpert, J.E., Nierenberg, A.A., Fava, M., 2004. Psychosocial functioning during the treatment of major depressive disorder with fluoxetine. Journal of Clinical Psychopharmacology 24, 507-511

64. Papakostas, G.I., 2009. Major depressive disorder: psychosocial impairment and key considerations in functional improvement. American Journal of Managed Care 15, S316-S321.

65. Paykel, E.S., Ramana, R., Cooper, Z., Hayhurst, H., Kerr, J., Barocka, A., Residual symptoms after partial remission: an important outcome in depression. Psychological Medicine 25, 1171–1180.

66. Perlis, R.H., Brown, E., Baker, R.W., Nierenberg, A.A., 2006. Clinical features of bipolar depression versus major depressive disorder in large multicenter trials. American Journal of Psychiatry 163, 225–231

67. Pintor, L., Gastó, C., Navarro, V., Torres, X., Fañanas, L., 2003. Relapse of major depression after complete and partial remission during a 2-year follow-up. Journal of Affective Disorders 73, 237–244.

68. Pintor, L., Torres, X., Navarro, V., Gastó, C., 2004. Is the type of remission after a major depressive episode an important risk factor to relapses in a 4-year follow up? Journal of Affective Disorders 82, 291–296.

69. Prince, M., Patel, V., Saxena, S., Maj, M., Maselko, J., Phillips, M.R., Rahman, A., 2007. No health without mental health. Lancet 370, 859-877.

70. Riso, L.P., Thase, M.E., Howland, R.H., Friedman, E.S., Simons, A.D., Tu, X.M., 1997. A prospective test of criteria for response, remission, relapse, recovery, and recurrence in depressed patients treated with cognitive behavior therapy. Journal of Affective Disorders 43, 131-142.

71. Roca, M., García-Toro, M., García-Campayo, J., Vives, M., Armengol, S., García-García, M., Asensio, D., Gili, M., Clinical differences between early and late remission in depressive patients. Journal of Affective Disorders 134, 235-241

72. Romera, I., Fernández-Pérez, S., Montejo, A.L., Caballero, F., Caballero, L., Arbesú, J.Á., Delgado-Cohen, H., Desaiah, D., Polavieja, P., Gilaberte, I., 2010. Generalized anxiety disorder, with or without co-morbid major depressive disorder, in primary care: prevalence of painful somatic symptoms, functioning and health status. Journal of Affective Disorders 127, 160-168.

73. Romera, I., Perez, V., Menchón, J.M., Delgado-Cohen, H., Polavieja, P., Gilaberte, I., 2010. Social and occupational functioning impairment in patients in partial versus complete remission of a major depressive disorder episode. A six-month prospective epidemiological study. European Psychiatry 25, 58-65.

74. Romera, I., Pérez, V., Menchón, J.M., Polavieja, P., Gilaberte, I., 2011. Optimal cutoff point of the Hamilton Rating Scale for Depression according to normal levels of social and occupational functioning. Psychiatry Research 186, 133-137.

75. Romera, I., Pérez, V., Menchón, J.M., Schacht, A., Papen, R., Neuhauser, D., Abbar, M., Svanborg, P., Gilaberte, I., 2012. Early switch strategy in patients with major depressive disorder: A double-blind, randomized study. Journal of Clinical Psychopharmacology 32, 479-486

76. Romera, I., Pérez, V., Menchón, J.M., Schacht, A., Papen, R., Neuhauser, D., Abbar, M., Picard, H., Gilaberte, I., 2012. Early vs. conventional switching of antidepressants in patients with MDD and moderate to severe pain: A double-blind randomized study. Journal of Affective Disorders 143, 47-55

77. Romera, I., Pérez, V., Gilaberte, I., 2013. Remisión y funcionalidad en el trastorno depresivo mayor. Actas Españolas de Psiquiatria, en prensa.

78. Ruhé, H.G., Dekker, J.J., Peen, J., Holman, R., de Jonghe, F., 2005. Clinical use of the Hamilton Depression Rating Scale: is increased efficiency possible? A post hoc comparison of Hamilton Depression Rating Scale, Maier and Bech subscales, Clinical Global Impression, and Symptom Checklist-90 scores. Comprehensive Psychiatry 46, 417-427.

79. Rush, A.J., Kraemer, H.C., Sackeim, H.A., Fava, M., Trivedi, M.H., Frank, E., Ninan, P.T., Thase, M.E., Gelenberg, A.J., Kupfer, D.J., Regier, D.A., Rosenbaum, J.F., Ray, O., Schatzberg, A.F., 2006. ACNP Task Force. Report by the ACNP Task Force on response and remission in major depressive disorder. Neuropsychopharmacology 31, 841-53.

80. Salvador-Carulla, L., Bendeck, M., Fernández, A., Alberti, C., Sabes-Figuera, R., Molina, C., Knapp, M., 2011. Costs of depression in Catalonia (Spain). Journal of Affective Disorders 132, 130-138.

81. Sheehan, D.V., Harnett-Sheehan, K., Raj, B.A., 1996. The measurement of disability. International Clinical Psychopharmacology 11, S89-S95

82. Sheehan, D.V., Harnett-Sheehan, K., Spann, M.E., Thompson, H.F., Prakash, A., 2011. Assessing remission in major depressive disorder and generalized anxiety disorder clinical trials with the discan metric of the Sheehan disability scale. International Clinical Psychopharmacology 26, 75-83.

83. Simon, G.E., Revicki, D., Heiligenstein, J., Grothaus, L., VonKorff, M., Katon, W.J., Hylan, T.R., 2000. Recovery from depression, work productivity and health care costs among primary care patients. General Hospital Psychiatry 22, 153-162.

84. Simon, G.E., Goldberg, D.P., Von Korff, M., Ustün, T.B., 2002. Understanding cross-national differences in depression prevalence. Psychological Medicine 32, 585-594.

85. Sobocki, P., Ekman, M., Agren, H., Runeson, B., Jönsson, B., 2006. The mission is remission: health economic consequences of achieving full remission with antidepressant treatment for depression. International Journal of Clinical Practice 60, 791–798.

86. Sokero, T.P., Melartin, T.K., Rytsälä, H.J., Leskelä, U.S., Lestelä-Mielonen, P.S., Isometsä, E.T., 2005. Prospective study of risk factors for attempted suicide among patients with DSM-IV major depressive disorder. British Journal of Psychiatry 186, 314–318.

87. Solomon, D.A., Leon, A.C., Endicott, J., Mueller, T.I., Coryell, W., Shea, M.T., Keller, M.B., 2004. Psychosocial impairment and recurrence of major depression. Comprehensive Psychiatry 45, 423-430.

88. Solomon, D.A., Leon, A.C., Coryell, W., Mueller, T.I., Posternak, M., Endicott, J., Keller, M.B., 2008. Predicting recovery from episodes of major depression. Journal of Affective Disorders 107, 285–291

89. Trivedi, M.H., Corey-Lisle, P.K., Guo, Z., Lennox, R.D., Pikalov, A., Kim, E., 2009. Remission, response without remission, and nonresponse in major depressive disorder: Impact on functioning. International Clinical Psychopharmacology 24, 133-138

90. Taylor, D.J., Walters, H.M., Vittengl, J.R., Krebaum, S., Jarrett, R.B., 2009. Which depressive symptoms remain after response to cognitive therapy of depression and predict relapse and recurrence? Journal of Affective Disorders 123, 181-187.

91. Thase, M.E., Sloan, D.M., Kornstein, S.G., 2002. Remission as the critical outcome of depression treatment. Psychopharmacology Bulletin 36, S12-S25.

92. Trivedi, M.H., Rush, A.J., Wisniewski, S.R., Nierenberg, A.A., Warden, D, Ritz, L., Norquist, G., Howland, R.H., Lebowitz, B., McGrath, P.J., Shores-Wilson, K., Biggs, M.M., Balasubramani, G.K., Fava, M., STAR*D Study Team., 2006. Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: implications for clinical practice. American Journal of Psychiatry 163, 28-40.

93. Trivedi, M.H., 2009. Tools and strategies for ongoing assessment of depression: a measurement-based approach to remission. Journal of Clinical Psychiatry 70, Suppl 6, 26-31

94. Tylee, A., Gastpar, M., Lépine, J.P., Mendlewicz, J., 1999. DEPRES II (Depression Research in European Society II): a patient survey of the symptoms, disability and current management of depression in the community. DEPRES Steering Committee. International Clinical Psychopharmacology 14, 139-151.

95. Valladares, A., Dilla, T., Sacristán, J.A., 2009. Depression: a social mortgage. Latest advances in knowledge of the cost of the disease. Actas Españolas de Psiquiatria 37, 49–53.

96. World Health Organization Department of Mental Health and Substance Abuse Geneva, Switzerland. http://www.who.int/mental_health/evidence/icd_advisory_group_december_08_summary.pdf (acceso: 22-Junio-2012)

97. Yang, H., Chuzi, S., Sinicropi-Yao, L., Johnson, D., Chen, Y., Clain, A., Baer, L., McGrath, P.J., Stewart, J.W., Fava, M., Papakostas, G.I., 2010. Type of residual symptom and risk of relapse during the continuation/maintenance phase treatment of major depressive disorder with the selective serotonin reuptake inhibitor fluoxetine. European Archives of Psychiatry and Clinical Neuroscience 260, 145-150.

98. Zimmerman, M., Posternak, M.A., Chelminski, I., 2004. Defining Remission on the Montgomery-Asberg Depression Rating Scale. Journal of Clinical Psychiatry 65,163–168

99. Zimmerman, M., Posternak, M.A., Chelminski, I., 2005. Is the cutoff to define remission on the Hamilton Rating Scale for Depression too high? Journal of Nervous and Mental Disease 193, 170-175.

100. Zimmerman, M., McGlinchey, J.B., Posternak, M.A., Friedman, M., Attiullah, N., Boerescu, D., 2006a. How should remission from depression be defined? The depressed patient's perspective. American Journal of Psychiatry 163, 148-150.

101. Zimmerman, M., McGlinchey, J.B., Posternak, M.A., Friedman, M., Boerescu, D., Attiullah, N., 2006b. Discordance between self-reported symptom severity and psychosocial functioning ratings in depressed outpatients: implications for how remission from depression should be defined. Psychiatry Research 141, 185-191

102. Zimmerman, M., Posternak, M.A., Chelminski, I., 2007. Heterogeneity among depressed outpatients considered to be in remission. Comprehensive Psychiatry 48, 113-117.

103. Zimmerman, M., Galione, J.N., Attiullah, N., Friedman, M., Toba, C., Boerescu, D.A., Ragheb, M., 2011. Depressed patients' perspectives of 2 measures of outcome: the Quick Inventory of Depressive Symptomatology (QIDS) and the Remission from Depression Questionnaire (RDQ). Annals of Clinical Psychiatry 23, 208-212.

104. Zimmerman, M., Martinez, J., Attiullah, N., Friedman, M., Toba, C., Boerescu, D.A., Rahgeb, M., 2012a. Further evidence that the cutoff to define remission on the 17-item Hamilton Depression Rating Scale should be lowered. Depression and Anxiety 29, 159-165.

105. Zimmerman, M., Martinez, J.A., Attiullah, N., Friedman, M., Toba, C., Boerescu, D.A., Rahgeb, M., 2012b.Why do some depressed outpatients who are in remission according to the Hamilton Depression Rating Scale not consider themselves to be in remission? Journal of Clinical Psychiatry 73, 790-795.

VIII - PUBLICACIONES ADICIONALES

1. Romera I, Pérez V. Gilaberte I. Remisión y funcionalidad en el trastorno depresivo mayor. Actas Españolas de Psiquiatria, 2013, en prensa.

2. Romera I et al. Journal of Clinical Psychopharmacology 2012; 32: 479-486

3. Romera I et al. Journal of Affective Disorders 2012;143(1-3):47-55

REMISIÓN Y FUNCIONALIDAD EN EL TRASTORNO DEPRESIVO MAYOR

Nombre de los autores y afiliación

Romera I[a,b*], Perez V[c], Gilaberte I[a]

[a] Clinical Research Department, Lilly S.A., Madrid, Spain

[b] Universidad Autónoma de Barcelona, Spain

[c] Department of Psychiatry, Hospital de Sant Pau i de la Santa Creu. Barcelona, Universidad Autónoma de Barcelona, CIBERSAM, Spain

Información de contacto

Perez V, Hospital de Sant Pau i de la Santa Creu. C/Sant Antoni Maria Claret, 167. E-08025, Barcelona, Spain. +34.93.291.90.00. vperez@hsp.santpau.es

Gilaberte I, Clinical Research Department, Lilly, SA. Avenida de la Industria, 30. E-28108, Alcobendas-Madrid, Spain.
Tel.: +34.91.663.50.00. Fax: +34.91.663.52.31.
gilaberte_inmaculada@lilly.com

Título abreviado

Remisión y funcionalidad en depresión

Título en Ingles

Remission and functioning in major depressive disorder

Palabras clave

Remission, funtioning, depression

*Corresponding author and reprint requests

Irene Romera

Clinical Research Department

Lilly, SA

Avenida de la Industria, 30. Alcobendas E-28108. Madrid, Spain

Tel.: +34.91.663.50.00. Fax: +34.91.663.52.31

E- mail: romera_irene@lilly.com

Resumen

La evidencia procedente de numerosos estudios clínicos ha demostrado que el objetivo óptimo en el tratamiento de la depresión es la remisión. La remisión implicaría que los signos y síntomas de la enfermedad estén ausentes o prácticamente ausentes, lo cual se asocia típicamente con una vuelta a la funcionalidad diaria previa del paciente. La funcionalidad en depresión es un concepto amplio, que cubre diferentes dominios, existiendo numerosos instrumentos validados para su valoración que se revisan en este artículo. Asimismo, cada vez más se identifica que la recuperación de la funcionalidad al nivel pre-mórbido es un objetivo significativo adicional a la remisión sintomática. En este sentido, la recuperación de la funcionalidad se ha relacionado con un mejor pronóstico de la depresión, siendo también un objetivo clínico expresado por el paciente. Entre los factores contribuyentes a la recuperación funcional se encuentra la remisión completa de los síntomas, sin síntomas residuales, el mantenimiento de la remisión, calidad de la misma, así como que esta se produzca de una manera temprana. Con el fin de favorecer los resultados clínicos se hace necesaria la integración en la práctica clínica de la evaluación y búsqueda de no sólo la remisión sintomática sino también de la recuperación funcional.

Abstract

Evidence from numerous clinical studies has shown that the optimal objective for the treatment of depression is remission. Remission implies that the signs and symptoms of the disease are absent or virtually absent, which is typically associated with a return to the patient's previous daily functioning. Functioning in depression is a broad concept, covering different domains and there are many validated instruments for its assessment that are reviewed in this article. Also, the to its pre-morbid level is a significant target additional to symptomatic remission. In this sense, the recovery of functionality has been associated with better prognosis of recovery of functionality depression and is also a clinical goal expressed by the patient. Several factors, like complete remission of symptoms, with no residual symptoms, maintenance of remission, quality of remission, early remission, have been identified as contributors to functional recovery. To facilitate the clinical outcomes, integration into the clinical practice of the assessment and search of not only symptomatic remission but also the recovery of functionality is required.

REMISIÓN Y FUNCIONALIDAD EN EL TRASTORNO DEPRESIVO MAYOR

En los últimos años la evidencia procedente de numerosos estudios clínicos ha demostrado que el objetivo óptimo en el tratamiento de la depresión es la remisión.[1] Según las recomendaciones sobre remisión del grupo de trabajo de la American College of Neuropsychopharmacology (ACNP) publicadas en el 2006, el concepto de remisión implicaría que los signos y síntomas de la enfermedad estén ausentes o prácticamente ausentes, lo cual se asocia típicamente con una vuelta a la función diaria previa del paciente.[2] El término remisión también se ha equiparado a la presencia de "salud".[1] Al igual que en otras enfermedades médicas crónicas, el nivel de salud en depresión debería ser evaluado teniendo en cuenta la combinación de tres dominios clave: síntomas, estado funcional y cambios fisiopatológicos.[1] Dadas las limitaciones actuales sobre la valoración de los cambios fisiopatológicos, se propone que la mejor aproximación para la definición de remisión sería un sistema que primeramente tenga en cuenta los síntomas, pero también tenga en cuenta el funcionamiento psicosocial del paciente. Es decir, el resultado óptimo del tratamiento sería la remisión con ausencia de síntomas y ausencia de alteración funcional, o restablecimiento de una funcionalidad completa y saludable.[1]

Pero, ¿qué entendemos por funcionalidad? Este es un concepto amplio, que cubre diferentes dominios. Áreas comúnmente incluidas en el concepto de funcionalidad son la funcionalidad laboral (la habilidad de llevar a cabo tareas y actividades asociadas al trabajo), el cuidado personal, la funcionalidad social (relaciones personales), familiar y cognitiva. Una definición aceptada del término de funcionalidad es "la capacidad de realizar actividades o tareas en el modo en el que se espera o se requiere".[3] De esta forma, funcionalidad social se ha definido como "la capacidad del individuo de realizar y llevar a cabo un papel social normal"[4] o "la interacción del individuo con su entorno y la capacidad de llevar a cabo su papel dentro del mismo".[5]

Cabe señalar que el término funcionalidad a veces se confunde con otros como satisfacción o calidad de vida. Funcionalidad, así como satisfacción, se considera componente de la calidad de vida. Sin embargo funcionalidad y satisfacción pueden variar de forma independiente, por ejemplo, un paciente puede tener alteración de la funcionalidad en diferentes dominios y estar

satisfecho con su situación en la vida. Más aun, la satisfacción es subjetiva y por tanto valorada por el paciente y la funcionalidad puede ser medida de una forma más objetiva.[3]

Medición de la funcionalidad: instrumentos de evaluación

Existen numerosos instrumentos validados que se usan comúnmente en estudios clínicos para valorar la funcionalidad en pacientes con depresión (Tabla 1).

Una de las escalas más utilizadas, tanto en estudios en depresión como en ansiedad, es la escala de discapacidad de Sheehan (Sheehan Disability Scale; SDS). Incluye tres áreas funcionales: trabajo-estudios, social y familiar. Los pacientes puntúan en una escala de cero a diez en qué medida los síntomas han interferido en cada uno de estos dominios.[6] Se considera como niveles normales de funcionalidad una puntuación total menor o igual a 6[7] siendo 30 es el peor nivel de funcionalidad posible. [6] La SDS es un instrumento bien establecido que tiene la ventaja de ser breve, fácil de usar y que al mismo tiempo ha demostrado ser sensible al cambio.[3]

Otra escala comúnmente utilizada es la escala SOFAS (Social and Occupational Functioning Scale), también conocida como EEASL (escala de evaluación de la actividad social y laboral). Esta escala se deriva del DSM-IV-TR (manual diagnóstico y estadístico de los trastornos mentales, cuarta edición revisada); el clínico o investigador indica el nivel de funcionamiento del individuo en un continuo de 1 a 100 (100 es funcionalidad óptima). Mide puramente la alteración funcional sin tener en cuenta los síntomas.[8] Los intervalos más altos de la SOFAS, 81-90 y 91-100, describen a individuos sin psicopatología significativa y que presentan muchos rasgos de salud mental positiva, un amplio rango de intereses, efectividad social, etc. Por lo que una puntuación ≥80 en la SOFAS se considera un nivel normal de funcionamiento [9]. La SOFAS tiene la ventaja de ser un instrumento ampliamente utilizado, sencillo y rápido de usar valorando la funcionalidad de una manera global. Al mismo tiempo tiene la desventaja de no incluir dominios específicos de valoración de la funcionalidad.

Aunque hay numerosas escalas para la evaluación de la funcionalidad cabe mencionar que estas se emplean fundamentalmente en investigación siendo escaso su empleo en la práctica clínica

habitual. Esto contrasta con lo defendido por el DSM-IV, que sugiere que los síntomas de la depresión mayor deben ser evaluados en términos de su impacto funcional en el área social, ocupacional, u otro tipo de área relevante y recomienda el uso de una evaluación global de la funcionalidad.[8] Más aún, los aspectos funcionales parece que van a cobrar más relevancia en el DSM-V así como en el CIE-11 y se están haciendo esfuerzos para facilitar su evaluación (WHO, Department of Mental Health). Es posible que el bajo uso de escalas específicas de valoración de la funcionalidad sea en parte reflejo del mayor peso que tradicionalmente han tenido los aspectos sintomáticos sobre los funcionales en el campo de la investigación en depresión. La existencia de nuevas escalas de reciente aparición, como la RDQ (Remission from Depression Questionnaire), sencillas de aplicar, aceptadas por el paciente, pueden ser estrategias a tener en cuenta para la mejora del proceso de evaluación del paciente.[10] En este sentido la RDQ tiene la ventaja de incluir los dominios que el paciente considera importantes para su recuperación. De forma que se incluyen aspectos sintomáticos, funcionales, relacionados con la salud metal positiva, con la capacidad de afrontamiento, así como con el bienestar y la satisfacción.[10]

Por último, uno de los aspectos fundamentales a considerar es la evaluación de la funcionalidad pre-mórbida, donde el uso de escalas queda limitado y la entrevista clínica es la herramienta con mayor peso. La evaluación de la funcionalidad pre-mórbida cobra un papel relevante para establecer objetivos terapéuticos concretos y adaptados a cada paciente.

Remisión sintomática y recuperación funcional como objetivo terapéutico

Actualmente la remisión sintomática es el objetivo principal del tratamiento del episodio de depresión. Sin embargo, la recuperación de la funcionalidad al nivel pre-mórbido se identifica cada vez más como un objetivo significativo adicional a la remisión sintomática.[11]

La recuperación de la funcionalidad se ha relacionado con un mejor pronóstico de la depresión. Estudios observacionales de seguimiento han encontrado una asociación significativa entre alteración de la funcionalidad y mayor duración de los episodios.[12] También se ha visto que la presencia de alteración en el funcionamiento, tras la recuperación del episodio, se relaciona con más recurrencias depresivas.[13] Más recientemente, este mismo autor examinó, en una amplia

muestra de pacientes con depresión mayor, la relación entre el funcionamiento psicosocial y la recuperación, mediante un estudio observacional de 20 años de seguimiento. La recuperación se definió como al menos 8 semanas consecutivas sin síntomas de depresión o únicamente uno o dos síntomas de intensidad leve. La alteración funcional se asoció de forma significativa con una menor probabilidad de recuperación del episodio de depresión mayor.[14]

La recuperación funcional también es un objetivo clínico expresado por el paciente con depresión. Zimmerman[15] estudió qué factores definían la remisión del episodio desde el punto de vista del paciente. Para ello, preguntó a 535 pacientes con depresión sobre la importancia de 16 factores para determinar si la depresión estaba en remisión. La funcionalidad social y laboral, expresada como el retorno al nivel normal de funcionamiento, fue un factor identificado como "muy importante" por el 74% de los pacientes. Incluso por encima de la ausencia de síntomas depresivos, donde el 70% de los pacientes lo consideraron como un factor "muy importante". Pero además de la recuperación funcional, la presencia de salud mental positiva (optimismo y autoconfianza) y volver a sentirse como antes, como uno mismo, se identificaron como "muy importantes" por el paciente.[15] Es decir, desde el punto de vista del paciente, dentro de sus expectativas de recuperación, la recuperación funcional se considera altamente relevante.

Factores que se asocian a la recuperación funcional

Pero, ¿cuáles son los factores que se asocian a la mejoría o restauración funcional en los pacientes con depresión mayor? Los factores identificados que contribuyen incluyen, entre otros, la trayectoria funcional del paciente a lo largo de la vida, la efectividad del tratamiento, el tiempo hasta la remisión, la duración de la remisión y la calidad de la remisión[11] (Tabla 2).

La funcionalidad pre-mórbida es un factor determinante del nivel de funcionalidad después del episodio. Ormel y colaboradores,[16] en un estudio prospectivo poblacional realizado en Holanda, examinaron la funcionalidad psicosocial antes, durante y después del primer episodio de depresión. Observaron que tras la remisión, la funcionalidad regresó a los niveles pre-mórbidos. La alteración funcional psicosocial reflejaba en gran parte la continuación de la alteración funcional pre-mórbida.

En relación con la efectividad del tratamiento se hace necesaria una resolución completa y sostenida de los síntomas depresivos para alcanzar la restauración del funcionamiento. De forma que las aproximaciones terapéuticas efectivas que lleven al mantenimiento de un estado de remisión sintomática aumentarían las opciones de recuperación funcional del paciente.[11] El estudio de Miller y colaboradores[17] evidenció esta relación. Aquellos pacientes que alcanzaron la remisión (HAMD-17 ≤7) tras 12 semanas de tratamiento agudo, presentaban mejor funcionalidad que aquellos que solo respondieron (reducción en la puntuación total del HAMD-17 mayor o igual al 50%). Asimismo, tuvieron niveles similares de funcionamiento que una población control sin depresión. En un estudio más reciente, Papakostas evaluó la funcionalidad en un grupo de pacientes con depresión que recibieron tratamiento con fluoxetina durante 8 semanas. Al igual que en el estudio de Miller, la mejoría funcional fue mayor en aquellos pacientes que alcanzaron la remisión (HAMD-17 ≤7) vs. los que únicamente respondieron.[18]

Respecto a la resolución completa de los síntomas depresivos y restauración del funcionamiento, cabe destacar un estudio observacional llevado a cabo en España.[19] Romera y colaboradores estudiaron el impacto de la presencia de síntomas residuales tras el tratamiento agudo, remisión parcial, en el pronóstico funcional del paciente con depresión. Para ello se siguió de forma prospectiva durante 6 meses a dos cohortes emparejadas de pacientes: pacientes en remisión completa (n=146) y pacientes en remisión parcial (n=146). Se evidenció que la presencia de síntomas residuales tras el tratamiento agudo se asoció a una alteración significativa de la funcionalidad, la cual persistió incluso tras 6 meses de tratamiento de continuación. De forma que únicamente un 47% de los pacientes en remisión parcial alcanzaron una funcionalidad normal vs. un 77% de los pacientes en remisión completa (Figura 1). Tras el periodo de seguimiento, los niveles medios de funcionalidad para los pacientes en remisión parcial estaban significativamente por debajo de la normalidad (76,2 [12,3] remisión parcial vs. 84,6 [9,4] remisión completa; p<0,0001). Durante los 6 meses de seguimiento, los pacientes en remisión parcial estuvieron más tiempo de baja por enfermedad que los pacientes en remisión completa (63 vs. 20 días, respectivamente; p<0,001), lo que se asoció a un mayor coste.

Respecto al tiempo hasta la remisión, una respuesta más temprana, así como una remisión temprana, se asoció significativamente a una mayor mejoría funcional.[18, 20] Cabe señalar el estudio de Ciudad y colaboradores, recientemente realizado en España sobre una amplia muestra

de pacientes con un episodio de depresión mayor seguidos durante 1 año. Este estudio evidenció que la respuesta temprana era el factor más fuertemente asociado a la mejoría funcional. Del mismo modo, la remisión temprana, dentro de las primeras 6 semanas de tratamiento, fue un factor fuertemente asociado a la mejoría funcional. En los pacientes con una remisión temprana se observaron de manera global rangos normales de funcionamiento tan pronto como a las 6 semanas. Mientras que en aquellos que no alcanzaron la remisión temprana se requirió un año hasta alcanzar niveles normales de funcionamiento.

La duración y el mantenimiento de la remisión son factores que también contribuyen a la restauración funcional. Furukawa y colaboradores [21] encontraron que el funcionamiento mejoraba con la mejoría sintomática, pero sin embargo, no se alcanzaron niveles normales de funcionamiento hasta pasados unos meses de remisión sintomática. Es decir, estos resultados parecen indicar que la recuperación funcional va "retrasada" con respecto a la recuperación sintomática. Por otro lado, el mantenimiento de la remisión, evitar perder este estatus asintomático, también se hace imprescindible. La pérdida de la remisión no solamente contribuye a un empeoramiento del funcionamiento sino también a un aumento del riesgo de recaída y de recurrencia, por tanto perdiéndose la recuperación funcional.[11]

Por último, la calidad o grado de la remisión también se ha asociado a la recuperación funcional. Incluso en pacientes que están en remisión se han encontrado diferencias significativas en cuanto al grado de funcionamiento.[22-24] Un análisis realizado en 292 pacientes de España con trastorno depresivo mayor, para encontrar el punto de corte óptimo en la escala HAMD-17 que mejor predecía niveles normales de funcionamiento social y ocupacional, mostró que una puntuación ≤5 maximizó la sensibilidad y especificidad, en comparación con otras puntuaciones.[23] La puntuación media de la SOFAS para los pacientes con una puntuación de 0-5 en la HAMD-17 fue de 85,2 (CI 95%: 83,9-86,6), dentro de los niveles considerados normales. Sin embargo, para los pacientes con una puntuación de 6-7, la media de la SOFAS fue de 79,5 (CI 95%: 76,7-82,3), por debajo del rango considerado como normal. Zimmerman y colaboradores observaron que los pacientes que puntuaban igual o menos de 2 en la HAMD-17 comunicaron menor disfunción psicosocial que aquellos con una puntuación entre 3 y 7.[22] Este mismo autor, en un estudio reciente realizado en 274 pacientes con depresión en remisión (HAMD-17 ≤7), encontró resultados similares.[24] Los pacientes con puntuaciones 0-2 en la HAMD-17 tenían niveles

significativamente mejores de funcionamiento psicosocial, calidad de vida y una mayor satisfacción con su salud mental, en comparación con pacientes con puntuaciones de 3-7.[24] Se han encontrado resultados similares usando otros instrumentos como la escala de Montgomery-Asberg.[25] Por lo tanto, cuando no solo los síntomas sino también la recuperación de la función social y laboral se tienen en cuenta, el punto de corte tradicional de la HAMD-17 podría considerarse demasiado alto, es decir, una puntuación HAMD-17 ≤7 no implica necesariamente niveles normales de funcionalidad.[23]

Por tanto, dentro de los factores que se asocian a la recuperación funcional, la remisión de los síntomas es un factor clave. Pero no solamente cobra relevancia alcanzar la remisión sintomática, sino que para maximizar las opciones de recuperación funcional esta remisión tendría que producirse en un corto periodo de tiempo, tan pronto como fuera posible. Asimismo, la "calidad" o grado de remisión es un factor a tener en cuenta, ya que incluso en remisión, menores puntuaciones en las escalas sintomáticas se asocian a una mejor funcionalidad. Por último, esta remisión sintomática tiene que mantenerse en el tiempo para consolidar la recuperación funcional y disminuir el riesgo de recaída, por tanto disminuir el riesgo de pérdida funcional.

Limitaciones

Debido a que el presente artículo no es una revisión sistemática no se recogen todos los posibles trabajos publicados sobre remisión y funcionalidad en depresión. Sin embargo, el objetivo de este trabajo es realizar una revisión general y de utilidad para la práctica clínica.

Conclusiones

La remisión sintomática es el objetivo principal del tratamiento del episodio de depresión. Sin embargo, la recuperación de la funcionalidad al nivel pre-mórbido se identifica cada vez más como un objetivo clave, adicional a la remisión sintomática. Entre los factores contribuyentes a la recuperación funcional se encuentra la remisión completa de los síntomas, sin síntomas residuales, así como que esta se produzca de una manera temprana. Con el fin de favorecer los resultados clínicos se hace necesaria la integración en la práctica asistencial de la evaluación y búsqueda de no sólo la remisión sintomática sino también de la recuperación funcional.

Bibliografia

1. Keller MB. Past, present, and future directions for defining optimal treatment outcome in depression: remission and beyond. JAMA 2003;289(23):3152-60.
2. Rush AJ, Kraemer HC, Sackeim HA, Fava M, Trivedi MH, Frank E, et al.; ACNP Task Force. Report by the ACNP Task Force on response and remission in major depressive disorder. Neuropsychopharmacology 2006;31(9):1841-53.
3. Endicott J, Dorries KM. Functional outcomes in MDD: established and emerging assessment tools. Am J Manag Care 2009;15(11 Suppl):S328-34.
4. Hirschfeld RM, Montgomery SA, Keller MB, Kasper S, Schatzberg AF, Möller HJ, et al. Social functioning in depression: a review. J Clin Psychiatry 2000;61(4):268-75.
5. Bosc M, Dubini A, Polin V. Development and validation of a social functioning scale, the Social Adaptation Self-evaluation Scale. Eur Neuropsychopharmacol 1997;7(Suppl 1):S57-70:discussion S71-3.
6. Sheehan DV, Harnett-Sheehan K, Raj BA. The measurement of disability. Int Clin Psychopharmacol 1996;11(Suppl 3):89-95.
7. Sheehan DV, Harnett-Sheehan K, Spann ME, Thompson HF, Prakash A. Assessing remission in major depressive disorder and generalized anxiety disorder clinical trials with the discan metric of the Sheehan disability scale. Int Clin Psychopharmacol 2011;26(2):75-83.
8. Goldman HH, Skodol AE, Lave TR. Revising axis V for DSM-IV: a review of measures of social functioning. Am J Psychiatry 1992;149(9):1148-56.
9. Spitzer RL, Gibbon M, Endicott J. Global Assessment Scale (GAS), Global Assessment of Functioning (GAF) Scale, Social and Occupational Functioning Assessment Scale (SOFAS). Mental Health Status, Functioning and Disability Measures. In: First MB, editor. Handbook of psychiatric measures, 1st ed. Washington DC, USA: American Psychiatric Association; 2000. p. 96-100.
10. Zimmerman M, Galione JN, Attiullah N, Friedman M, Toba C, Boerescu DA, et al. Depressed patients' perspectives of 2 measures of outcome: the Quick Inventory of

Depressive Symptomatology (QIDS) and the Remission from Depression Questionnaire (RDQ). Ann Clin Psychiatry 2011;23(3):208-12.

11. Papakostas GI. Major depressive disorder: psychosocial impairment and key considerations in functional improvement. Am J Manag Care 2009;15(11 Suppl):S316-21.
12. Leon AC, Solomon DA, Mueller TI, Turvey CL, Endicott J, Keller MB. The Range of Impaired Functioning Tool (LIFE-RIFT): a brief measure of functional impairment. Psychol Med 1999;29(4):869-78.
13. Solomon DA, Leon AC, Endicott J, Mueller TI, Coryell W, Shea MT, et al. Psychosocial impairment and recurrence of major depression. Compr Psychiatry 2004;45(6):423-30.
14. Solomon DA, Leon AC, Coryell W, Mueller TI, Posternak M, Endicott J, et al. Predicting recovery from episodes of major depression. J Affect Disord 2008;107(1-3):285-91.
15. Zimmerman M, McGlinchey JB, Posternak MA, Friedman M, Attiullah N, Boerescu D. How should remission from depression be defined? The depressed patient's perspective. Am J Psychiatry 2006;163(1):148-50.
16. Ormel J, Oldehinkel AJ, Nolen WA, Vollebergh W. Psychosocial disability before, during, and after a major depressive episode: a 3-wave population-based study of state, scar, and trait effects. Arch Gen Psychiatry 2004;61(4):387-92.
17. Miller IW, Keitner GI, Schatzberg AF, Klein DN, Thase ME, Rush AJ, et al. The treatment of chronic depression, part 3: psychosocial functioning before and after treatment with sertraline or imipramine. J Clin Psychiatry 1998;59(11):608-19.
18. Papakostas GI, Petersen T, Denninger JW, Tossani E, Pava JA, Alpert JE, et al. Psychosocial functioning during the treatment of major depressive disorder with fluoxetine. J Clin Psychopharmacol 2004;24(5):507-11.
19. Romera I, Perez V, Menchón JM, Delgado-Cohen H, Polavieja P, Gilaberte I. Social and occupational functioning impairment in patients in partial versus complete remission of a major depressive disorder episode. A six-month prospective epidemiological study. Eur Psychiatry 2010;25(1):58-65.
20. Ciudad A, Álvarez E, Roca M, Baca E, Caballero L, García de Polavieja P, et al. Early response and remission as predictors of good outcome of a major depressive episode at

12-month follow-up: a prospective, longitudinal, observational study. J Clin Psychiatry 2012;73(2):185-91.

21. Furukawa TA, Takeuchi H, Hiroe T, Mashiko H, Kamei K, Kitamura T, et al. Symptomatic recovery and social functioning in major depression. Acta Psychiatr Scand 2001;103(4):257-61.
22. Zimmerman M, Posternak MA, Chelminski I. Is the cutoff to define remission on the Hamilton Rating Scale for Depression too high? J Nerv Ment Dis 2005;193(3):170-5.
23. Romera I, Pérez V, Menchón JM, Polavieja P, Gilaberte I. Optimal cutoff point of the Hamilton Rating Scale for Depression according to normal levels of social and occupational functioning. Psychiatry Res 2011;186(1):133-7.
24. Zimmerman M, Martinez J, Attiullah N, Friedman M, Toba C, Boerescu DA, et al. Further evidence that the cutoff to define remission on the 17-item Hamilton Depression Rating Scale should be lowered. Depress Anxiety 2012;29(2):159-65.
25. Zimmerman M, Posternak MA, Chelminski I. Defining remission on the Montgomery-Asberg depression rating scale. J Clin Psychiatry 2004;65(2):163-8.

Instrumento	Número de items	Dominios incluidos
Escala de evaluación de la actividad social y laboral (EEASL)	Único	Social Laboral
Escala de discapacidad de Sheehan (Sheehan Disability Scale; SDS)	3	Social y actividades de ocio Laboral(remunerado-estudiante-tareas del hogar) Relaciones con familia, role dentro de la familia
Escala de Ajuste Social Social Adjustment Scale (SAS)	48	Trabajo (remunerado, hogar, estudiante) Actividades de ocio y sociales Papel marital Papel parental Papel como un miembro en la familia
Escala de valoración global de la funcionalidad (Global Assessment of Functioning scale; GAF)	Único	Severidad de los síntomas y alteración funcional
WHODAS (World Health Organization Disability Assessment Schedule)	36	Cognición Mobilidad Autocuidado Interacciones interpersonales Actividades Participación en la sociedad
Escala de productividad laboral de Endicott	25	Eficiencia y productividad laboral

Longitudinal Interval Follow-up Evaluation-Range of Impaired Functioning Tool	9	Trabajo Relaciones interpersonales Satisfacción general con el funcionamiento Recreación
Life Functioning Questionnaire	14	Tareas en el trabajo/escuela Tareas en el hogar Tiempo de ocio con familia Tiempo de ocio con amigos
Health of the Nation Outcomes Scales	12	Comportamiento Disfunción Síntomas Funcionamiento social

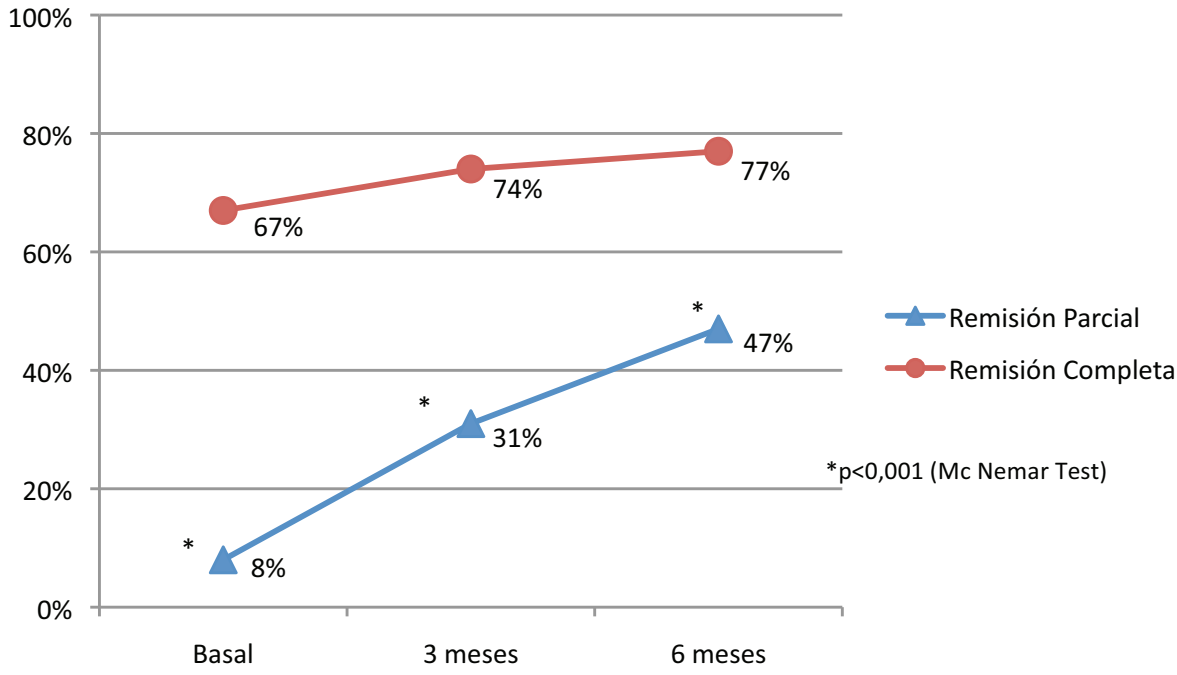
Adaptado de Endicott J et al. 2009

Tabla 1: Instrumentos de medición de la funcionalidad

Trayectoria funcional del paciente a lo largo de la vida
Co-morbilidad médica y psiquiátrica
Efectividad del tratamiento
Remisión completa de los síntomas depresivos
Tiempo hasta la remisión
Duración o mantenimiento de la remisión
Calidad o grado de la remisión

Adaptado de Papakostas GI. 2009

Tabla 2. Factores asociados a la recuperación funcional



SOFAS: Social and Occupational Functioning Assessment Scale.

*p<0,001 (Mc Nemar Test)

Figura 1. Porcentaje de pacientes que alcanzaron una funcionalidad normal (SOFAS≥80) en el momento basal, a los 3 y a los 6 meses.

From: Revista Actas Españolas de Psiquiatría [mailto:revista.actas@fundacionlopezibor.es]
Sent: jueves, 10 de enero de 2013 14:17
To: IRENE CRISTINA ROMERA
Subject: RE: Ref 1731 Remisión y funcionalidad en el trastorno depresivo mayor

Estimados autores:

Gracias por haber confiado en las Actas Españolas de Psiquiatría al enviar su trabajo titulado "Remisión y funcionalidad en el trastorno depresivo mayor".

Le informamos que el Comité Editorial ha decidido la publicación de su artículo sin mayores modificaciones. A partir de este momento puede citar su artículo como "publicado, en prensa". No obstante, le pedimos que sea paciente en la espera de su publicación definitiva, que vendrá anunciada por el envío de las pruebas de imprenta para su corrección inmediata.

Atentamente.

Miquel Roca y María López-Ibor

Editores de Actas Españolas de Psiquiatría

Aida Navalón
Secretaria Técnica

Actas Españolas de **Psiquiatría**

FUNDACIÓN JUAN JOSÉ LÓPEZ-IBOR

C/ DR. JUAN JOSÉ LÓPEZ IBOR 2

28035 MADRID (ESPAÑA)

Tel.: (+34) 91 373 91 19

Fax: (+34) 91 316 27 49

De: IRENE CRISTINA ROMERA [mailto:romera_irene@lilly.com]
Enviado el: miércoles, 02 de enero de 2013 18:22
Para: Revista Actas Españolas de Psiquiatría
CC: inmagilaberte@live.com
Asunto: RE: Ref 1731 Remisión y funcionalidad en el trastorno depresivo mayor

Estimados Editores de Actas Españolas de Psiquiatría,

Agradecemos que hayan considerado nuestro articulo para publicación así como el tiempo empleado en su valoración. Adjuntamos la nueva versión revisada incluyendo los comentarios y sugerencias de los revisores que consideramos han sido de gran utilidad.

Adjuntamos también la carta de respuesta a los revisores.

Atentamente,

Dra. Irene Romera

Departamento Medico Lilly, SA

From: Revista Actas Españolas de Psiquiatría [mailto:revista.actas@fundacionlopezibor.es]
Sent: miércoles, 26 de diciembre de 2012 11:55
To: IRENE CRISTINA ROMERA
Subject: RE: Ref 1731 Remisión y funcionalidad en el trastorno depresivo mayor

Estimados autores:

Gracias por haber confiado en las Actas Españolas de Psiquiatría al enviar su trabajo titulado "Remisión y funcionalidad en el trastorno depresivo mayor".

Su manuscrito ha sido estudiado por revisores independientes cuyos comentarios le adjuntamos. Aunque el artículo podría ser publicable en la revista, la opinión de los revisores ha sido crítica con algunos aspectos del artículo que deberán modificarse de acuerdo a las sugerencias realizadas por los mismos. Le rogamos por tanto que a la mayor brevedad envíe la nueva versión modificada del manuscrito, señalando los cambios realizados mediante subrayado y la respuesta a las observaciones de los revisores, para proceder a su reevaluación.

Atentamente.

Miquel Roca y María López-Ibor

Editores de Actas Españolas de Psiquiatría

Aida Navalón
Secretaria Técnica

Actas Españolas de **Psiquiatría**

FUNDACIÓN JUAN JOSÉ LÓPEZ-IBOR

C/ DR. JUAN JOSÉ LÓPEZ IBOR 2

28035 MADRID (ESPAÑA)

Tel.: (+34) 91 373 91 19

Fax: (+34) 91 316 27 49

www.actaspsiquiatria.es

www.fundacionlopezibor.es

De: Revista Actas Españolas de Psiquiatría [mailto:revista.actas@fundacionlopezibor.es]
Enviado el: miércoles, 12 de septiembre de 2012 10:12
Para: 'IRENE CRISTINA ROMERA'
Asunto: Ref 1731 Remisión y funcionalidad en el trastorno depresivo mayor

Estimados autores:

Le confirmo que hemos recibido correctamente su artículo “REMISIÓN Y FUNCIONALIDAD EN EL TRASTORNO DEPRESIVO MAYOR”

Le comunico que la referencia con la que reconoceremos su artículo es 1731.

El uso de esta referencia para la identificación de su trabajo nos ayudará a ser más efectivos a la hora de localizarlo.

A continuación revisaremos su trabajo y le comunicaremos a la mayor brevedad posible si su artículo cumple las normas y si es apto para la publicación en nuestra revista.

Muchas gracias por confiarnos su trabajo.

Atentamente,

Aida Navalón
Secretaria Técnica

Actas Españolas de **Psiquiatría**

FUNDACIÓN JUAN JOSÉ LÓPEZ-IBOR

C/ DR. JUAN JOSÉ LÓPEZ IBOR 2

28035 MADRID (ESPAÑA)

Tel.: (+34) 91 373 91 19

Fax: (+34) 91 316 27 49

www.actaspsiquiatria.es

www.fundacionlopezibor.es

De: IRENE CRISTINA ROMERA [mailto:romera_irene@lilly.com]
Enviado el: martes, 11 de septiembre de 2012 15:24
Para: revista.actas@fundacionlopezibor.es
CC: Victor Pérez Sola; INMACULADA GILABERTE; IRENE FREGENAL
Asunto: Articulo: Remisión y funcionalidad en el trastorno depresivo mayor

Estimado comité editorial de *Actas Españolas de Psiquiatría*:

Me complace adjuntarles nuestro manuscrito titulado: *Remisión y funcionalidad en el trastorno depresivo mayor.*

Los aspectos funcionales asociados a la remisión del episodio depresivo están cobrando una mayor relevancia. Sin embargo, los estudios clínicos al respecto son muy escasos. A través de este articulo se revisa la relación existente entre la remisión clínica y funcional procedente de la evidencia de los estudios en este campo.

Creemos que el contenido de este artículo tiene un interés relevante para la práctica clínica y por lo tanto solicitamos su revisión por parte del comité editorial, esperando que lo encuentren adecuado para su publicación en *Actas Españolas de Psiquiatría*.

Todos los autores han contribuido a la elaboración de este estudio, así como a la revisión crítica del mismo y están de acuerdo con el envío del manuscrito para su publicación.

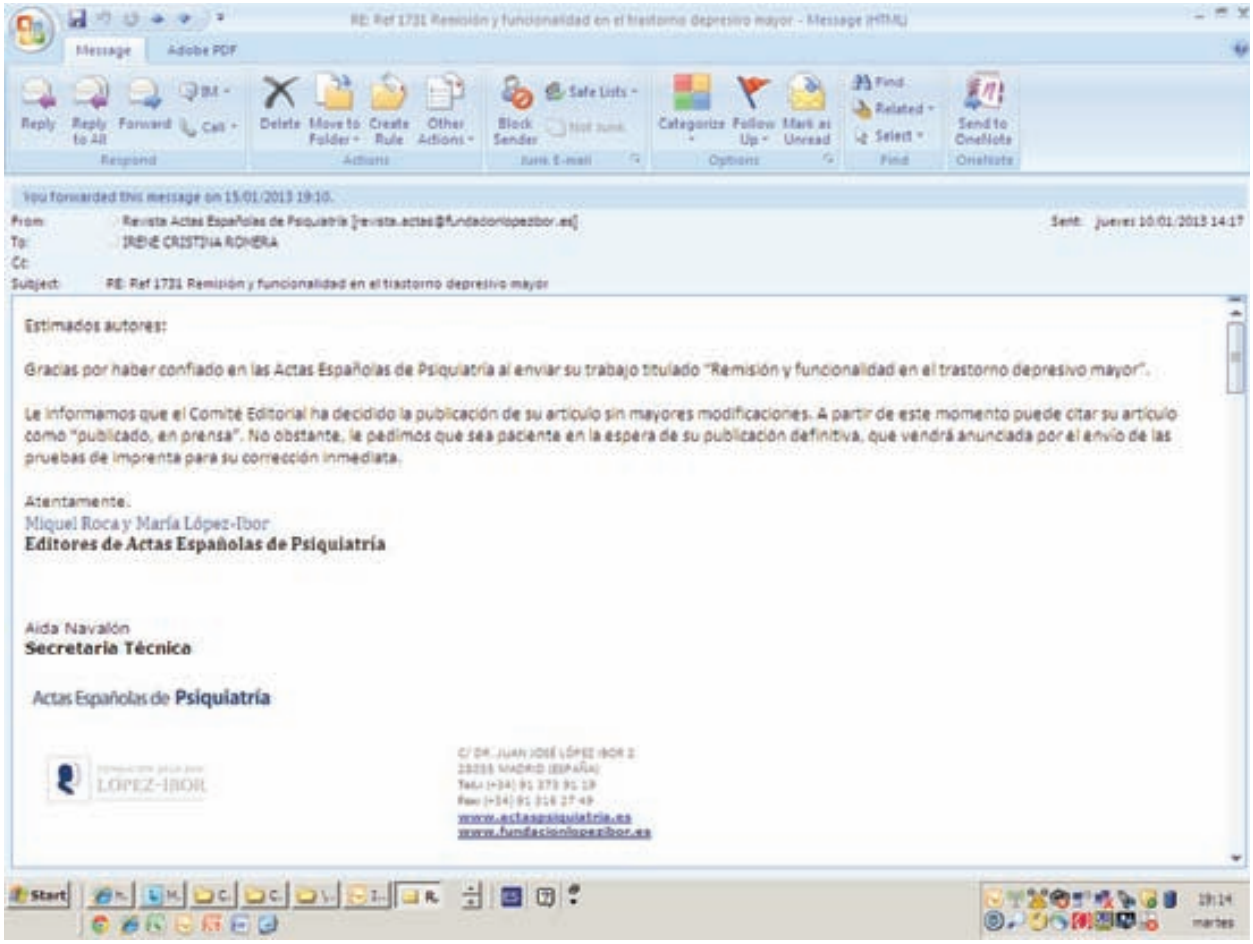
Quiero agradecerles por adelantado el tiempo que dediquen a la revisión de nuestro artículo. Por favor, no duden en ponerse en contacto conmigo para cualquier cosa que puedan necesitar.

Reciban un cordial saludo,

Dra. Irene Romera

Departamento de Investigación Clínica, Lilly España

romera_irene@lilly.com



You forwarded this message on 15/01/2013 19:10.

From: Revista Actas Españolas de Psiquiatría [revista.actas@fundacionlopezibor.es] Sent: jueves 10/01/2013 14:17
To: IRENE CRISTINA RONERA
Cc:
Subject: RE: Ref 1731 Remisión y funcionalidad en el trastorno depresivo mayor

Estimados autores:

Gracias por haber confiado en las Actas Españolas de Psiquiatría al enviar su trabajo titulado "Remisión y funcionalidad en el trastorno depresivo mayor".

Le informamos que el Comité Editorial ha decidido la publicación de su artículo sin mayores modificaciones. A partir de este momento puede citar su artículo como "publicado, en prensa". No obstante, le pedimos que sea paciente en la espera de su publicación definitiva, que vendrá anunciada por el envío de las pruebas de imprenta para su corrección inmediata.

Atentamente.
Miquel Roca y María López-Ibor
Editores de Actas Españolas de Psiquiatría

Aida Navalón
Secretaria Técnica

Actas Españolas de **Psiquiatría**

LÓPEZ-IBOR

C/ DR. JUAN JOSÉ LÓPEZ IBOR 2
28035 MADRID (ESPAÑA)
Tel.: (+34) 91 373 91 19
Fax: (+34) 91 316 27 49
www.actasespsiquiatria.es
www.fundacionlopezibor.es

Early Switch Strategy in Patients With Major Depressive Disorder

A Double-Blind, Randomized Study

Irene Romera, MD,† Victor Pérez, MD, PhD,‡ Jose Manuel Menchón, MD, PhD,§ Alexander Schacht, PhD,|| Rita Papen, FH,|| Doris Neuhauser, MSc,¶ Mocrane Abbar, MD,# Pär Svanborg, MD, PhD,**†† and Inmaculada Gilaberte, MD, PhD‡‡*

Objective: Antidepressant switch is a commonly used strategy in the absence of an adequate response, but optimum timing is not well established. We compared the efficacy of an early and a conventional antidepressant switch strategy in patients with major depressive disorder.

Methods: Patients with no or minimal improvement (<30% reduction in baseline 17-item Hamilton Depression Rating Scale [$HAMD_{17}$] score) after 4 weeks on escitalopram 10 mg/d were randomized to either early switch strategy with duloxetine 60 to 120 mg/d for 12 weeks (arm A) or conventional switch strategy (arm B): 4 further weeks on escitalopram 10 to 20 mg/d; then, in case of nonresponse (response, ≥50% reduction in $HAMD_{17}$), switch to duloxetine 60 to 120 mg/d for 8 weeks, or continued escitalopram in responders. Co-primary end points were time to confirmed response and remission ($HAMD_{17}$, ≤7). Strategies were compared using Kaplan-Meier, logistic regression, and repeated-measures analyses.

Results: Sixty-seven percent (566 of 840) of patients showed no or minimal improvement and were randomized to arm A (282 patients) or arm B (284 patients). No between-strategy differences in time to confirmed response (25% Kaplan-Meier estimates, 3.9 vs 4.0 weeks, P = 0.213) or remission (6.0 vs 7.9 weeks, P = 0.075) were found. Rates of confirmed responders were similar (64.9% vs 64.1%); however, more patients randomized to early switch achieved confirmed remission (43.3% vs 35.6%; P = 0.048).

Conclusions: Although no differences in the primary end points were found, a higher remission rate was seen with the early switch strategy. Our findings suggest that further investigations to reevaluate the conventional approach to antidepressant switch strategy would be worthwhile.

From *Eli Lilly and Company, Madrid; †Universidad Autónoma de Barcelona, Departamento de Psiquiatría; ‡Hospital de Sant Pau i de la Santa Creu. UAB, CIBERSAM; §Hospital Universitari de Bellvitge-IDIBELL, University of Barcelona. CIBERSAM, Hospitalet de Llobregat, Barcelona, Spain; ||Eli Lilly and Company, Bad Homburg, Germany; ¶Eli Lilly and Company, Vienna, Austria; #Hôspital Carémeau, Nîmes, France; **Eli Lilly and Company, Solna; ††Department of Clinical Neuroscience, Psychiatry Section, Karolinska Institutet, Stockholm, Sweden; and ‡‡Eli Lilly and Company, Madrid, Spain.

Received May 3, 2011; accepted after revision January 24, 2012.

Reprints: Irene Romera, MD, Clinical Research Physician Neuroscience, Medical Department, Eli Lilly and Company, Avenida de la Industria, 30, 28108-Alcobendas, Madrid, Spain (e-mail: romera_irene@lilly.com).

This study was funded by Eli Lilly and Company.

The data described in this article were partially presented at the International Forum on Mood and Anxiety Disorders in Vienna, Austria, on November 17–19, 2010.

This trial was registered on ClinicalTrials.gov on December 16, 2008 (Identifier: NCT00810069; *http://clinicaltrials.gov/ct2/show/NCT00810069?term=hmgd&rank=1*).

Supplemental digital content is available for this article. Direct URL citation appears in the printed text and is provided in the HTML and PDF versions of this article on the journal's Web site (www.psychopharmacology.com).

ISSN: 0271-0749
DOI: 10.1097/JCP.0b013e31825d9958

Key Words: major depressive disorder, early switch strategy, antidepressant switch, treatment optimization, major depressive disorder treatment strategies

(*J Clin Psychopharmacol* 2012;32: 479–486)

Antidepressant switch is a commonly used strategy in patients with initial selective serotonin reuptake inhibitor (SSRI) treatment failure.[1–8] Because it is generally believed that the clinical onset of antidepressant activity is delayed,[9] a "watchful waiting approach" while optimizing the dose of the initial treatment is often adopted before switching antidepressants.[10–12] Therefore, it is common practice to wait for about 6 to 12 weeks until response is assessed and the antidepressant switch is conducted. This practice also reflects the clinical belief that antidepressant switch could be associated with loss of the initial therapeutic effect. Despite the widespread use of this antidepressant switch strategy, randomized controlled trials (RCTs) evaluating its timing are lacking and the recommended timelines in guidelines vary.[13]

Contrary to the hypothesis of a delayed onset of antidepressant activity, several post hoc studies have consistently shown that lack of early improvement reduces the chance of response or remission.[14–17] Nierenberg et al[15] reported that lack of improvement (<30% decrease in the Hamilton Rating Scale for Depression [HAMD]) after 4 weeks of treatment was associated with an 80% chance of nonresponse after 8 weeks. Similarly, Szegedi et al[16] found that lack of early improvement in the first 3 weeks of treatment was associated with more than 90% chance of nonresponse. This finding was confirmed in a larger patient population.[17] Recently, Lin et al[18] concluded from their study in Han Chinese patients with major depressive disorder (MDD) that patients with less than a 50% symptom reduction in HAMD during the first 4 weeks of treatment are unlikely to reach a final stable response at week 6. After performing a systematic review, Nakajima et al[19] came to the conclusion that the timing of antidepressant switch must be adequately evaluated.

To our knowledge, no published RCT has evaluated the optimal timing for antidepressant switch. Only preliminary findings from a controlled study support the theory that patients with absence of early improvement might benefit from an antidepressant switch as early as after two weeks of treatment.[20] The present RCT compared an early antidepressant switch strategy with the conventional switch strategy in patients with MDD. In the early switch strategy, antidepressant switch was done after 4 weeks of treatment; in the conventional switch strategy, it was done after an additional 4 weeks of treatment and dose optimization, thus reflecting routine clinical practice. Escitalopram was chosen as the initial SSRI treatment because it has been shown to be the most serotonin transporter–selective compound,[21] with some evidence for superior efficacy compared with other SSRIs.[12,22] Because of

its different mechanism of action, duloxetine was chosen as the antidepressant after the switch. We tested the hypothesis that an early switch strategy results in shorter times to confirmed response and confirmed remission in patients with no or minimal improvement after 4 weeks of escitalopram treatment.

METHODS

Patients at 60 centers in 11 European countries were enrolled between November 2008 and March 2010 in this phase IV, multicenter, randomized, double-blind, parallel-group study in MDD. It was approved by the institutional review boards at each center and was conducted according to the International Conference on Harmonization guideline on good clinical practice.[23]

Patients

Male or female outpatients aged 18 years or older who met the diagnostic criteria for single or recurrent episodes of MDD according to the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition-Text Revision* (American Psychiatric Association, 1994) were enrolled. Patients had to have a 17-item HAMD ($HAMD_{17}$) score of 19 or higher and a Clinical Global Impression-Severity (CGI-S) score of 4 or higher at baseline. Antidepressant treatment, except with escitalopram or duloxetine, was permitted until study entry. In compliance with the duloxetine and escitalopram Summary of Product Characteristics, there was no upper age limit.

Exclusion criteria were any current primary Axis I disorder other than MDD; a previous diagnosis of bipolar disorder, schizophrenia, or other psychotic disorders; a history of substance abuse or dependence in the past year, excluding nicotine and caffeine; a diagnosis of dementia, Alzheimer's disease, organic brain syndrome; a cognitive impairment that prevents the patient from understanding the study; serious or unstable medical conditions; serious suicidal risk; pregnancy or nursing; history of lack of response to duloxetine or escitalopram or any contraindication against the use of these medications. Patients who required initiation or discontinuation of psychotherapy before enrollment or during the study or those on antidepressant treatment who showed a treatment response before study entry were also excluded.

Written informed consent was obtained before conducting any study procedures.

Study Design

All patients were treated with 10 mg/d escitalopram for 4 weeks (study period I [SPI]; Supplemental Appendix A, Supplemental Digital Content 1, http://links.lww.com/JCP/A132). At the end of SPI, patients who showed an improvement (≥30% reduction in baseline score of the $HAMD_{17}$) were withdrawn from the study and treated according to routine clinical practice. All other patients were randomized 1:1 in double-blind fashion to an early or conventional switch strategy (study period II [SPII]) using a central interactive voice response system. Patients in the early switch strategy arm (arm A) received a flexible dose of duloxetine (60–120 mg/d; starting dose, 60 mg/d) for up to 12 weeks. In the conventional switch strategy arm (arm B), patients continued to take escitalopram (flexible dose, 10–20 mg/d) for a further 4 weeks, then nonresponders (<50% reduction in baseline $HAMD_{17}$ score) were switched to duloxetine (60–120 mg/d; starting dose, 60 mg/d) for 8 weeks (subgroup B_1) whereas responders continued on escitalopram (10–20 mg/d) for 8 weeks (subgroup B_2). During SPII, the dose could be adjusted according to efficacy and tolerability at the investigator's discretion. Permitted doses were 10 or 20 mg/d for escitalopram and 60 or 120 mg/d for duloxetine based on the European Summary of Product Characteristics. Patients who switched from escitalopram to duloxetine took the lower dose of duloxetine (60 mg/d) for at least the first 2 weeks.

Patients who completed SPII or who discontinued the study prematurely after randomization could enter an optional 2-week double-blind tapering phase (study period III [SPIII]). Patients who achieved confirmed remission before the end of SPII were allowed to leave the study and were considered to have completed the study.

The study design aimed to compare two different approaches regarding timelines for conducting an antidepressant switch strategy. Therefore, comparisons were between patients randomized to early switch strategy (arm A) and patients randomized to conventional switch strategy (arm B) until the end of SPII. The conventional switch strategy includes escitalopram dose optimization (weeks 4-8; SPII), assessment of response (week 8; SPII), and based on this, switch to duloxetine (subgroup B_1) or continue on escitalopram (subgroup B_2) from weeks 8 to 16 (SPII). This conventional switch strategy aimed to mimic clinical practice.

Measures

The co-primary efficacy outcome measures were time to confirmed response and time to confirmed remission based on the $HAMD_{17}$ total score.[24,25] Secondary efficacy measures included $HAMD_{17}$ total and subscale scores, Quick Inventory of Depressive Symptomatology–Self-Reported Score (QIDS-SR),[26] and CGI-S.[27] Functional improvement was assessed by the Sheehan Disability Scale (SDS)[28,29] and quality of life by the EuroQol-5 dimensions (EQ-5D) questionnaire.[30] In addition, pain was assessed on a visual analog scale; any pain visual analog scale results are planned to be described in a separate manuscript. Study measures were collected by the investigators. The $HAMD_{17}$ and CGI-S were collected at baseline (week 0), at week 4 (randomization), and every 2 weeks thereafter. A telephone-based structured interview for the $HAMD_{17}$ was performed by the investigators at weeks 5, 7, 9, 11, 13, and 15. This structured interview was the same as used by Trivedi et al.[31] If the phone interview showed response or remission, a $HAMD_{17}$ score was collected at the site on the same day or the day after to capture the time of response or remission as accurately as possible. If a patient met the response or remission criteria for the first time at a scheduled visit, the next scheduled telephone interview was replaced by a site visit to collect a confirmatory $HAMD_{17}$ score. Similarly, if a patient met response or remission criteria for the first time at the last study visit (week 16), an additional site visit to collect an $HAMD_{17}$ score was scheduled for the following week. Patients completed the QIDS-SR at weeks 5, 7, 9, 11, 13, and 15. Functioning and quality of life measures were collected at weeks 0, 4, 8, 12, and 16.

Spontaneously reported adverse events (AEs), vital signs, and concomitant medication were recorded at all visits. Height and weight were measured at baseline only.

Concomitant Medications

Benzodiazepines and hypnotics were allowed if taken more than 8 hours before the study visit. Anticonvulsants, antidepressants other than duloxetine or escitalopram, hypericum, antipsychotics, lithium, methyldopa, dopamine agonists, psychostimulants, triptans, and tramadol were not allowed.

Confirmed Response and Confirmed Remission Criteria

Confirmed response was defined as 50% or greater reduction in baseline total $HAMD_{17}$ score maintained for at least 2

consecutive weekly visits. Confirmed remission was defined as an $HAMD_{17}$ total score of 7 or less maintained for at least 2 consecutive weekly visits. The confirmation at the next consecutive visit was used to obtain a more robust assessment.

Statistical Analysis

The primary hypotheses of superiority of the early switch strategy (arm A) versus the conventional switch strategy (arm B) based on time to confirmed response and time to confirmed remission were tested consecutively following a gate-keeping strategy (see Supplemental Appendix B [Supplemental Digital Content 2, http://links.lww.com/JCP/A133] for sample size determination). Analyses of the co-primary efficacy variables included Kaplan-Meier estimation and corresponding descriptive statistics by switch strategy group. Generalized Wilcoxon tests with a 2-sided significance level of 0.05 were used to compare switch strategies (arm A vs arm B) based on data from the entire 12-week SPII. For further exploration, times to first response and first remission, irrespective of confirmation at the next consecutive visit, were analyzed using similar methods.

Statistical methods to analyze secondary outcomes included mixed models for repeated-measures (MMRM) analyses for $HAMD_{17}$ total and subscale scores, the QIDS-SR total score, and the CGI-S rating scale. The model included terms for switch strategy, country, visit, strategy-by-visit interaction, baseline score, and baseline-by-visit interaction. The covariance structure converging to the best fit for the analysis of the variable, as determined by Akaike's information criterion, was used in the model for all efficacy variables. Analyses of covariance with terms for switch strategy, country, and as applicable, the baseline score of the dependent variable were performed for the SDS total and item scores and the EQ-5D score, using last-observation-carried-forward.

Frequencies of patients with AEs, serious AEs (SAEs), and AEs leading to discontinuation were presented for SPI and by strategy arm for SPII (including AEs that occurred during SPIII) and were compared using Fisher's exact test. Vital signs were descriptively summarized.

RESULTS

Disposition of Patients

Eight hundred seventy-seven patients were screened at study entry, and 840 received escitalopram 10 mg/d. After 4 weeks, 566 patients (67%) did not achieve a reduction in the $HAMD_{17}$ baseline score of 30% or greater and were therefore randomized to either early switch strategy (arm A; 282 patients) or conventional switch strategy (arm B; 284 patients) (Fig. 1). The number of discontinuations during SPII was similar (arm A, 19.9%; arm B, 20.4%).

Demographic and Clinical Characteristics

Patient characteristics at baseline are summarized in Table 1. Overall mean baseline total scores for $HAMD_{17}$ (mean, 24.2), CGI-S (4.6), and SDS (19.9) indicated that patients had moderate to severe MDD. A chronic course (>6 months) of the current depressive episode was present in 20.5% of the patients.

Before study entry, 35.7% of patients were on antidepressant treatment; frequencies were balanced between strategy arms, with most commonly reported previous antidepressants being SSRIs (33.4% of patients overall) and serotonin noradrenalin reuptake inhibitors (14.8%). A previous psychiatric illness was reported for 8.0% of patients. At randomization (week 4), the overall mean total scores for $HAMD_{17}$ and CGI-S were 21.5 and 4.3, respectively.

Exposure to Treatment

Before the week 8 response assessment and nonresponders in arm B being switched to duloxetine, the mean study treatment dose was 80.5 mg/d duloxetine for patients randomized to the early switch strategy (arm A) and 16.7 mg/d escitalopram for those randomized to the conventional switch strategy (arm B). At the end of the study, the mean dose was 90.4 mg/d duloxetine for arm A, 79.4 mg/d duloxetine for subgroup B_1, and 17.4 mg/d escitalopram for subgroup B_2.

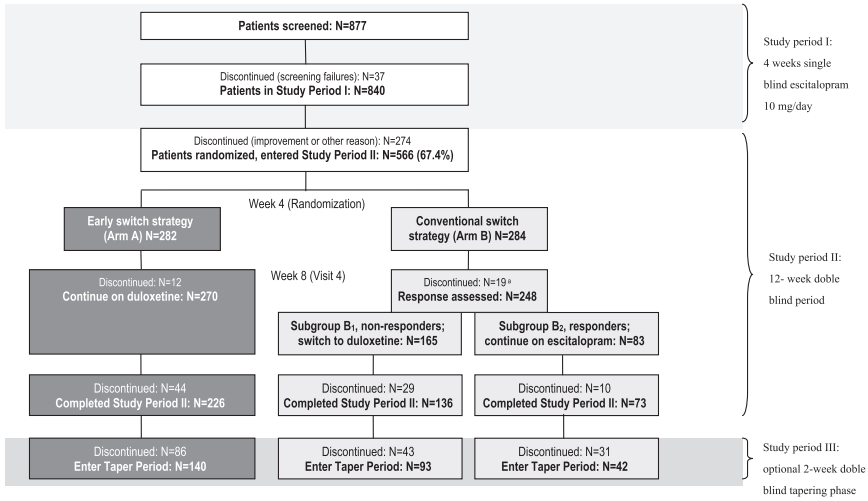


FIGURE 1. Patient disposition. N = number of patients. [a]In addition, 1 patient completed the study (remission criteria met) and 16 patients were discontinued because no treatment information was available. Early switch strategy: Patients were randomized to a flexible dose of duloxetine (60–120 mg/d) for 12 weeks. Conventional switch strategy: Patients were randomized to escitalopram treatment at flexible doses (10–20 mg/d) for 4 additional weeks; then at week 8, nonresponders (<50% baseline score reduction on the 17-item Hamilton Depression Rating Scale) were switched to duloxetine (60–120 mg/d) for 8 weeks (subgroup B_1), whereas responders continued on escitalopram (10–20 mg/d) during the same 8-week period (subgroup B_2).

TABLE 1. Baseline Demographics and Clinical Characteristics

	Early Switch Strategy (n = 282)	Conventional Switch Strategy (n = 284)	Overall (N = 566)
Age, y			
Mean (SD)	48.3 (13.5)	47.4 (12.7)	47.9 (13.1)
Median (range)	48.8 (19.3, 86.6)	48.4 (19.2, 73.9)	48.8 (19.2, 86.8)
Gender (n [%])			
Female	196 (69.5)	197 (69.4)	393 (69.4)
Male	86 (30.5)	87 (30.6)	173 (30.6)
No. patients with at least 1 previous episode (n [%])	220 (78.0)	212 (74.6)	432 (76.3)
No. previous episodes or exacerbations			
Mean (SD)	2.7 (3.3)	2.4 (2.5)	2.5 (3.0)
Median (range)	2.0 (0, 30.0)	2.0 (0, 12.0)	2.0 (0, 30.0)
Time since the first episode, y			
Mean (SD)	9.7 (11.1)	8.9 (10.4)	9.3 (10.8)
Median (range)	6.3 (−0.4, 58.7)	5.0 (−0.4, 49.0)	5.8 (−0.4, 58.7)
No. patients with current episode >6 mo (n [%])	67 (23.8)	49 (17.3)	116 (20.5)
$HAMD_{17}$ total score			
Mean (SD)	24.0 (3.6)	24.4 (3.8)	24.2 (3.7)
Median (range)	24.0 (19.0, 35.0)	24.0 (19.0, 40.0)	24.0 (19.0, 40.0)
QIDS-SR total score			
Mean (SD)	16.4 (3.8)	16.7 (3.4)	16.5 (3.6)
Median (range)	16.0 (4.0, 25.0)	17.0 (4.0, 25.0)	17.0 (4.0, 25.0)
CGI-S score			
Mean (SD)	4.6 (0.59)	4.6 (0.6)	4.6 (0.6)
Median (range)	5.0 (4.0, 6.0)	5.0 (4.0, 6.0)	5.0 (4.0, 6.0)
SDS total score			
Mean (SD)	19.9 (5.1)	19.9 (5.5)	19.9 (5.3)
Median (range)	21.0 (4.0, 30.0)	21.0 (0.0, 30.0)	21.0 (0.0, 30.0)

CGI-MDD-S indicates Clinical Global Impression-Major Depressive Disorder-Severity; $HAMD_{17}$, 17-item Hamilton Depression Rating Scale; N, total number of patients; n, number of patients with no missing value; SDS, Sheehan Disability Scale.

Time to Confirmed Response and Confirmed Remission

No statistically significant differences between strategies were seen for time to confirmed response ($P = 0.213$, Wilcoxon test) or time to confirmed remission ($P = 0.075$, Wilcoxon test) based on data from the entire 12-week SPII. However, statistically significant differences in favor of the early switch strategy (arm A) were observed at week 12 (Kaplan-Meier estimates for the rate of confirmed remitters, 0.37 [arm A] and 0.27 [arm B]; $P = 0.025$) and week 14 (0.43 [arm A] and 0.34 [arm B]; $P = 0.046$). The time at which 25% of patients had reached a confirmed response was 3.9 weeks in patients randomized to the early switch strategy (arm A) and 4.0 weeks in those randomized to the conventional switch strategy (arm B) (Fig. 2). Corresponding times for confirmed remission were 6.0 weeks (arm A) and 7.9 weeks (arm B) after randomization. The median time to confirmed response was 6.4 weeks in arm A and 8.0 weeks in arm B. The median time to confirmed remission for arm A was 12.9 weeks and could not be estimated for arm B because of the low number of patients with confirmed remission (Fig. 2).

The number of patients achieving a confirmed response at the end of the study based on the $HAMD_{17}$ was similar between strategies (Fig. 3). The number of patients achieving confirmed remission, however, was statistically significantly higher with the early switch strategy (43.3%) than with the conventional switch strategy (35.6%; $P = 0.048$) (Fig. 3).

Results from the sensitivity analysis of time to first response and time to first remission, irrespective of whether response or remission was confirmed at the next consecutive visit, were consistent with the primary efficacy analysis results.

Secondary Efficacy Outcomes

Differences in least square (LS) mean $HAMD_{17}$ total scores between strategies were statistically significant in favor of the early switch strategy (arm A) at week 8 (difference, −1.0; 95% confidence interval, −1.94, −0.06; $P = 0.038$) and week 10 (difference, −1.0; 95% confidence interval, −1.99, −0.04; $P = 0.041$) based on the MMRM analysis. At week 16, LS mean $HAMD_{17}$ total scores were similar between strategies (Table 2). In the MMRM analyses of the HAMD subscales, statistically significant differences between strategies in LS means favoring patients randomized to the early switch strategy were seen for some subscales and some time points between weeks 8 and 14 but not at the end of the study (week 16) (Table 2).

No statistically significant between-strategy differences were seen at end point in QIDS-SR, CGI-S, SDS, or EQ-5D analyses.

Safety and Tolerability Findings

During SPI, when all patients were treated with escitalopram 10 mg, 247 (29.4%) patients had at least 1 AE, and for 171 (20.4%) patients, at least 1 AE was considered related to escitalopram treatment. Forty-five (5.4%) patients discontinued

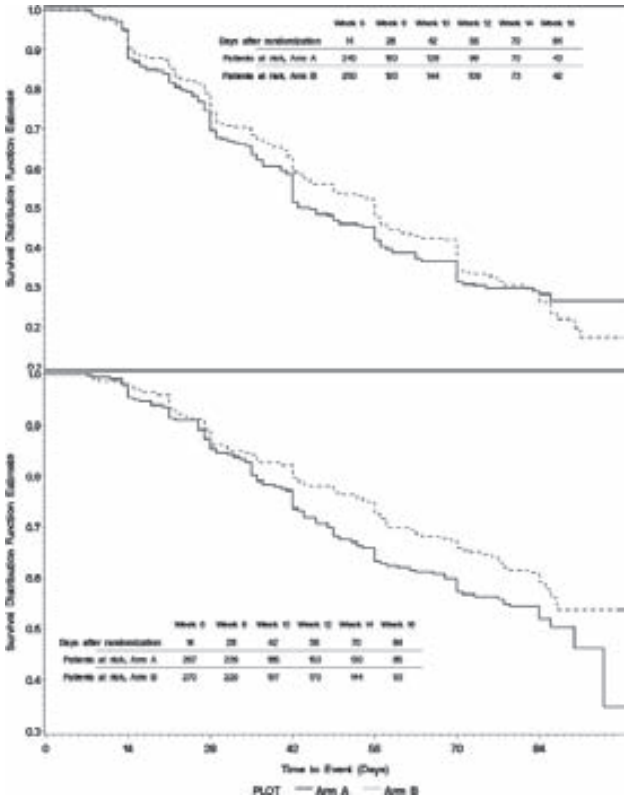


FIGURE 2. Kaplan-Meier curves for confirmed response (top) and remission (bottom) based on the 17-item Hamilton Depression Rating Scale (study period II). Time to event shown as days since randomization (ie, day 0 corresponds to week 4).

because of an AE and 4 (0.5%) patients reported an SAE; none of these were considered drug related.

During SPII (including SPIII), 25.2% of patients in the early switch strategy arm (arm A) and 22.9% in the conventional switch strategy arm (arm B) reported at least 1 drug-related AE; 2.8% (arm A) and 2.1% (arm B) discontinued the study because of an AE (Table 3). The AEs occurring in 4% or more patients in any strategy arm were headache, nausea, hyperhidrosis, and nasopharyngitis. Statistically significantly ($P < 0.05$) more patients in arm A than in arm B reported nausea (5.0% vs 1.8%, $P = 0.038$ [Fisher exact test]) and hot flushes (1.8% vs 0%, $P = 0.030$). No relevant findings were seen for vital signs.

DISCUSSION

To our knowledge, this is the first double-blind RCT to investigate the impact of timing of antidepressant switch in patients not showing an adequate early improvement on antidepressant treatment. Patients with MDD who had not improved after 4 weeks with escitalopram 10 mg/d were randomly allocated to either an early switch strategy with duloxetine or a conventional switch strategy. The latter strategy involved dose optimization of escitalopram treatment for an additional 4 weeks, followed by switch to duloxetine for nonresponders or continued escitalopram treatment for responders. We did not find statistically significant differences between the two strategies for time to confirmed response or time to confirmed remission. However, a significantly higher proportion of patients randomized to the early switch strategy achieved confirmed remission.

Current guidelines do not agree on when switching antidepressants is appropriate.[10,12] The most common initial strategy is to watch and wait while optimizing the dose. Several authors have advocated a more dynamic approach, including earlier switching for patients showing inadequate improvement.[17,32] Despite this, no RCTs have been conducted to evaluate the timing of antidepressant switch. Retrospective studies have shown a low chance of achieving a response by the end of 8 weeks' treatment in patients with no improvement in the HAMD total score of at least 30% after 4 weeks' treatment.[15,16] We therefore conducted this RCT to evaluate the efficacy of an early versus a conventional switch strategy.

Time to confirmed response was chosen as one of our primary variables because we think that the advantage of an early switch strategy should be measured when clinical symptoms improve. In addition, remission and, particularly, early remission are associated with better long-term outcomes.[33–38] We therefore included time to confirmed remission as our second primary end point to capture the full range of clinically relevant benefits of an early switch strategy.

Although between-strategy differences for the primary end points were not statistically significant, the early switch strategy did result in a statistically significantly higher rate of patients with clinical remission at the end of the study (43% vs 35%; $P = 0.048$). The statistically significant difference in remission rates of 8% (absolute) in the present study might be considered modest; however, it might be relevant from a clinical point of view. Furthermore, significant differences in remission rates are rarely reported in individual clinical trials comparing antidepressants and are much more often seen in meta–analyses.[39–41]

Interestingly, although our sample was composed of patients who did not improve after 4 weeks of initial antidepressant treatment, remission rates with either strategy were greater than those reported in the Sequenced Treatment Alternatives to Relieve Depression (STAR-D) trial.[31] This might be because of the different characteristics of the studied populations. In contrast to the STAR-D trial, our study was conducted in 11 European countries, and patients had fewer psychiatric comorbidities, although depression severity and chronicity were similar. A further explanation may be the different antidepressants and treatment strategies used. Whereas a conventional or watchful waiting approach of citalopram dose optimization for 14 weeks was used in the STAR-D trial, our study was more dynamic, even in the conventional strategy arm, where most of the patients were switched to the second antidepressant because of nonresponse after 8 weeks of escitalopram treatment optimization.

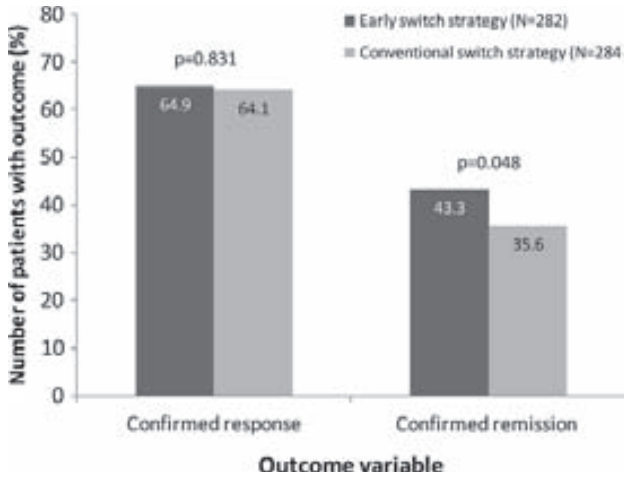


FIGURE 3. Overall rates for confirmed response and confirmed remission based on the 17-item Hamilton Depression Rating Scale (study period II). *P* values from logistic regression (adjusted for country).

TABLE 2. HAMD Total Score and Subscale Scores-Mixed Models for Repeated-Measures Analysis (Study Period II)

	Early Switch Strategy (n = 282)		Conventional Switch Strategy (n = 284)		Difference Between LS Means		
Visit	**LS Mean**	**95% CI**	**LS Mean**	**95% CI**	**Estimate**	**95% CI**	***P****
Total score							
Wk 6	17.35	(16.55, 18.14)	17.86	(17.06, 18.66)	−0.51	(−1.44, 0.41)	0.276
Wk 8	14.50	(13.69, 15.30)	15.49	(14.68, 16.30)	−1.00	(−1.94, −0.06)	**0.038**
Wk 10	12.39	(11.57, 13.22)	13.41	(12.58, 14.24)	−1.01	(−1.99, −0.04)	**0.041**
Wk 12	11.24	(10.39, 12.10)	12.21	(11.36, 13.07)	−0.97	(−2.00, 0.06)	0.064
Wk 14	9.81	(8.92, 10.70)	10.70	(9.81, 11.59)	−0.89	(−1.97, 0.20)	0.110
Wk 16	9.45	(8.53, 10.37)	9.54	(8.62, 10.45)	−0.09	(−1.22, 1.05)	0.882
Core mood subscale score							
Wk 6	6.43	(6.06, 6.79)	6.64	(6.27, 7.00)	−0.21	(−0.63, 0.21)	0.331
Wk 8	5.06	(4.69, 5.43)	5.64	(5.27, 6.01)	−0.58	(−1.01, −0.15)	**0.009**
Wk 10	4.23	(3.85, 4.60)	4.69	(4.31, 5.07)	−0.46	(−0.91, −0.01)	**0.043**
Wk 12	3.73	(3.34, 4.12)	4.25	(3.86, 4.64)	−0.52	(−1.00, −0.05)	**0.031**
Wk 14	3.27	(2.86, 3.68)	3.64	(3.23, 4.04)	−0.36	(−0.87, 0.14)	0.158
Wk 16	3.07	(2.65, 3.49)	3.04	(2.62, 3.46)	0.03	(−0.49, 0.56)	0.899
Maier subscale score							
Wk 6	8.54	(8.10, 8.98)	8.88	(8.44, 9.32)	−0.34	(−0.85, 0.17)	0.194
Wk 8	7.00	(6.55, 7.44)	7.71	(7.26, 8.16)	−0.71	(−1.24, −0.19)	**0.008**
Wk 10	5.85	(5.39, 6.30)	6.54	(6.08, 7.00)	−0.70	(−1.24, −0.15)	**0.012**
Wk 12	5.21	(4.74, 5.69)	5.92	(5.45, 6.40)	−0.71	(−1.29, −0.13)	**0.016**
Wk 14	4.52	(4.02, 5.02)	5.05	(4.56, 5.55)	−0.53	(−1.14, 0.08)	0.088
Wk 16	4.29	(3.77, 4.80)	4.41	(3.90, 4.92)	−0.12	(−0.76, 0.51)	0.704
Anxiety/somatization subfactor score							
Wk 6	5.61	(5.31, 5.92)	5.89	(5.59, 6.20)	−0.28	(−0.64, 0.07)	0.119
Wk 8	4.90	(4.60, 5.21)	5.29	(4.98, 5.60)	−0.38	(−0.75, −0.02)	**0.039**
Wk 10	4.21	(3.90, 4.53)	4.63	(4.31, 4.95)	−0.42	(−0.80, −0.04)	**0.030**
Wk 12	3.85	(3.52, 4.18)	4.29	(3.95, 4.62)	−0.43	(−0.84, −0.03)	**0.035**
Wk 14	3.36	(3.02, 3.71)	3.80	(3.45, 4.15)	−0.43	(−0.86, −0.01)	**0.046**
Wk 16	3.24	(2.88, 3.60)	3.43	(3.08, 3.79)	−0.19	(−0.63, 0.25)	0.398
Retardation subfactor score							
Wk 6	6.04	(5.72, 6.36)	6.24	(5.92, 6.56)	−0.20	(−0.58, 0.17)	0.287
Wk 8	4.98	(4.66, 5.31)	5.41	(5.08, 5.73)	−0.42	(−0.81, −0.04)	**0.029**
Wk 10	4.24	(3.91, 4.58)	4.61	(4.27, 4.94)	−0.36	(−0.76, 0.03)	0.072
Wk 12	3.87	(3.52, 4.21)	4.29	(3.95, 4.64)	−0.43	(−0.84, −0.01)	**0.046**
Wk 14	3.44	(3.08, 3.80)	3.76	(3.40, 4.12)	−0.32	(−0.77, 0.12)	0.153
Wk 16	3.18	(2.81, 3.55)	3.25	(2.88, 3.62)	−0.07	(−0.53, 0.39)	0.763

**P* from mixed model for repeated measures that included terms for strategy, country, visit, strategy × visit interaction, baseline score, and baseline × visit interaction; $P < 0.05$ highlighted in bold.

CI indicates confidence interval; LS, least square; n, number of patients.

TABLE 3. Overview of Adverse Events (Study Periods II and III Combined)

	Early Switch Strategy (n = 282)		Conventional Switch Strategy (n = 284)	
Category	**n**	**%**	**n**	**%**
At least 1 AE	112	39.7	101	35.6
At least 1 drug-related AE	71	25.2	65	22.9
At least 1 SAE	8	2.8	4	1.4
At least 1 drug-related SAE	3	1.1	2	0.7
Discontinued because of AE	8	2.8	6	2.1

AE indicates adverse event; n, number of patients; SAE, serious adverse event.

Statistically significant differences in favor of the early switch strategy were also seen in LS mean values for the HAMD total score at weeks 8 and 10, as well as most of the HAMD subscales at weeks 8, 10, and 12. This does not support the clinical belief of loss of initial effect associated with antidepressant switch. Nevertheless, at the end of the study, between-strategy differences for these variables were minimal and not statistically significant. This may be because, at week 8, nonresponders to escitalopram dose optimization using the conventional switch strategy were switched to duloxetine. In contrast, for patients switched earlier to duloxetine, no further adjustment for nonresponse was planned during SPII. This suggests that in case of no or minimal improvement, in addition to conducting an early switch strategy, repeated and dynamic treatment interventions might also be necessary until the desired outcome is achieved.

The AE profile was similar for both strategies. Discontinuation rates because of AEs were low for both strategies. Thus, directly switching from escitalopram to duloxetine at an initial dose of 60 mg was well tolerated, as previously reported.[6]

Our study had several limitations. Only one third of patients showed an improvement after the initial 4 weeks of treatment with escitalopram 10 mg. This dose may have been too low in our population of patients with moderate to severe MDD[42]; however, it is the recommended starting dose. Furthermore, from a meta-analysis of 14 RCTs in patients with severe MDD treated with escitalopram, Baldwin et al[43] concluded that an observation period of at least 4 weeks is worthwhile before considering further intervention such as an escitalopram dose increase from 10 to 20 mg. The low rate of improved patients after 4 weeks may also explain the relatively high percentage of responders (33.5%) in the conventional switch strategy arm after optimizing the escitalopram dose.[42] The generalizability of our results is limited by the characteristics of our population. A structured assessment for the diagnosis of MDD was not used; however, all participating principal investigators were psychiatrists and the diagnosis was based on *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*, criteria. Duloxetine was the antidepressant medication that patients were switched to; it is uncertain whether our findings can be generalized to other antidepressants used after switching, including other SSRIs, and further studies with different agents are required. Our study exclusively evaluated the timing for conducting a switching strategy. Other studies would be required to evaluate this timing question for other strategies, such as augmentation or combination. The power to detect differences between time-to-event end points relies on the number of patients with the reference event. Therefore, the ability to detect differences for such an end point might be inferior to an end point that is measured for every patient, such as the HAMD total score, which would integrate the differences between the strategies over time and thus might be more powerful to detect smaller but still important differences between strategies.

In conclusion, this first double-blind RCT to compare the outcome of an early antidepressant switch strategy with the conventional approach in MDD patients with no or minimal early improvement calls the conventional approach into question. Our primary outcomes were inconclusive because the differences between time to confirmed response and time to confirmed remission were not statistically significant. However, more patients randomized to the early switch strategy achieved confirmed remission. These findings suggest that it is worthwhile to conduct further RCTs that reassess the conventional "watchful waiting" approach and substantiate our findings before recommendations for clinical practice can be made. Comparisons of strategies that involve not only early but also more dynamic treatment decisions throughout the whole acute treatment period would be of value to gain further insight into disease management and improvement of clinical outcome.

ACKNOWLEDGMENTS

The authors thank Maria Isabel Vazquez, Belen Yrureta-goyena, Pepa Polavieja, and Deborah Quail from Lilly for their help with the protocol development and study implementation; Dr James Russell, Dr David Perahia, Dr Jesús Hernandez from Eli Lilly and Dr José Antonio Sacristan from Lilly Spain for providing medical advice on the study design (Jesús Hernandez is currently working for the Centro de Investigación Médica Aplicada de la Universidad de Navarra, Spain); Ansgar Dressler and Wolfgang Jacob of Trilogy Writing & Consulting GmbH (Frankfurt, Germany) for providing medical writing support; Alistair Reeves for editing assistance; Dr Alonso Montoya from Lilly Spain for providing medical advice on the manuscript; and the principal investigators and the patients for their voluntary participation.

AUTHOR DISCLOSURE INFORMATION

Dr Victor Perez has received grant support from Eli Lilly, Lundbeck, Boehringer, Pfizer, AstraZeneca, and GlaxoSmithKline; has received honoraria from Servier, Eli Lilly, Bristol-Myers Squibb-Otsuka, GlaxoSmithKline, AstraZeneca, and Boehringer; has served as a consultant for and/or on advisory boards for Eli Lilly, Bristol-Myers Squibb, and AstraZeneca. Dr Jose M Menchón declares that he has received funding from the University of Barcelona, the Bellvitge University Hospital-IDIBELL, and from the Spanish Ministry of Science and Innovation, Instituto de Salud Carlos III, Centro de Investigación en Red de Salud mental (CIBERSAM). He has also received honoraria as a consultant from Almirall, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Janssen, Lundbeck, and Wyeth. Dr Mocrane Abbar has received honoraria from Pfizer, Roche, Lundbeck, Organon, Jansen, Novartis, Sanofi, Servier, Eli Lilly, Bristol-Myers Squibb-Otsuka, GlaxoSmithKline, Sanofi, AstraZeneca, Boehringer, and Wyeth; has served as a consultant for and/or on advisory boards for Sanofi, Eli Lilly, Bristol-Myers Squibb-Otsuka, GlaxoSmithKline, and AstraZeneca. Dr Irene Romera, Dr Alexander Schacht, Rita Papen, Doris Neuhauser, Dr Pär Svanborg, and Dr Inmaculada Gilaberte are employees of Eli Lilly. Dr Irene Romera is also an affiliate with the Universidad Autónoma de Barcelona, Departamento de Psiquiatría. Dr Pär Svanborg and Dr Alexander Schacht are a minor stockholder of Eli Lilly.

REFERENCES

1. Fava M, Papakostas GI, Petersen T, et al. Switching to bupropion in fluoxetine-resistant major depressive disorder. *Ann Clin Psychiatry.* 2003;15(1):17–22.
2. Fava M. Switching treatments for complicated depression. *J Clin Psychiatry.* 2010;71(2):e04.
3. Hirschfeld RM. The use of mirtazapine in difficult-to-treat patient populations. *Hum Psychopharmacol.* 2002;17(suppl 1):S33–S36.
4. Nierenberg AA, Papakostas GI, Petersen T, et al. Nortriptyline for treatment-resistant depression. *J Clin Psychiatry.* 2003;64(1):35–39.
5. Papakostas GI, Fava M, Thase ME. Treatment of SSRI-resistant depression: a meta-analysis comparing within- versus across-class switches. *Biol Psychiatry.* 2008;63(7):699–704.
6. Perahia DG, Quail D, Desaiah D, et al. Switching to duloxetine from selective serotonin reuptake inhibitor antidepressants: a multicenter trial comparing 2 switching techniques. *J Clin Psychiatry.* 2008;69(1):95–105.

7. Rush AJ, Trivedi MH, Wisniewski SR, et al. Bupropion-SR, sertraline, or venlafaxine-XR after failure of SSRIs for depression. *N Engl J Med*. 2006b;354(12):1231–1242.
8. Thase ME, Friedman ES, Howland RH. Venlafaxine and treatment-resistant depression. *Depress Anxiety*. 2000;12(suppl 1):55–62. [Review].
9. Quitkin FM, McGrath PJ, Stewart JW, et al. Chronological milestones to guide drug change: when should clinicians switch antidepressants? *Arch Gen Psychiatry*. 1996;53(9):785–792.
10. American Psychiatric Association. Practice Guideline for the Treatment of Patients With Major Depressive Disorder, Third Edition. Available at: http://psychiatryonline.org/guidelines.aspx. Accessed June 5, 2012.
11. Anderson IM, Nutt DJ, Deakin JF. Evidence-based guidelines for treating depressive disorders with antidepressants: a revision of the 1993 British Association for Psychopharmacology guidelines. British Association for Psychopharmacology. *J Psychopharmacol*. 2000;14:3–20.
12. National Institute of Healthy and Clinical Excellence. The Treatment and Management of Depression in Adults, in The British Psychological Society & The Royal College of Psychiatrists, 2010. Available at: http://www.nice.org.uk/nicemedia/live/12329/45896/45896.pdf. Accessed June 5, 2012.
13. Tadić A, Gorbulev S, Dahmen N, et al. Rationale and design of the randomised clinical trial comparing early medication change (EMC) strategy with treatment as usual (TAU) in patients with major depressive disorder–the EMC trial. *Trials*. 2010;11:21.
14. Nierenberg AA, McLean NE, Alpert JE, et al. Early nonresponse to fluoxetine as a predictor of poor 8-week outcome. *Am J Psychiatry*. 1995;152(10):1500–1503.
15. Nierenberg AA, Farabaugh AH, Alpert JE, et al. Timing of onset of antidepressant response with fluoxetine treatment. *Am J Psychiatry*. 2000;157:1423–1428.
16. Szegedi A, Muller MJ, Anghelescu I, et al. Early improvement under mirtazapine and paroxetine predicts later stable response and remission with high sensitivity in patients with major depression. *J Clin Psychiatry*. 2003;64(4):413–420.
17. Szegedi A, Jansen WT, van Willigenburg AP, et al. Early improvement in the first 2 weeks as a predictor of treatment outcome in patients with major depressive disorder: a meta-analysis including 6562 patients. *J Clin Psychiatry*. 2009;70(3):344–353.
18. Lin CH, Lane HY, Chen CC, et al. Early prediction of fluoxetine response for Han Chinese inpatients with major depressive disorder. *J Clin Psychopharmacol*. 2011;31(2):187–193.
19. Nakajima S, Suzuki T, Watanabe K, et al. Accelerating response to antidepressant treatment in depression: a review and clinical suggestions. *Prog Neuropsychopharmacol Biol Psychiatry*. 2010;34(2):259–264.
20. Nakajima S, Uchida H, Suzuki T, et al. Benefits of switching antidepressants following early nonresponse. *Eur Neuropsychopharmacol*. 2009;19:S407.
21. Owens MJ, Knight DL, Nemeroff CB. Second-generation SSRIs: human monoamine transporter binding profile of escitalopram and R-fluoxetine. *Biol Psychiatry*. 2001;50(5):345–350.
22. Cipriani A, Furukawa TA, Salanti G, et al. Comparative efficacy and acceptability of 12 new-generation antidepressants: a multiple-treatments meta-analysis. *Lancet*. 2009;373(9665):746–758.
23. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use. Guideline for Good Clinical Practice E6(R1), 1996. Available at: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6_R1/Step4/E6_R1__Guideline.pdf. Accessed June 5, 2012.
24. Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry*. 1960;23:56–62.
25. Hamilton M. Development of a rating scale for primary depressive illness. *Br J Soc Clin Psychol*. 1967;6:278–296.
26. Rush AJ, Trivedi MH, Ibrahim HM, et al. The 16-Item Quick Inventory of Depressive Symptomatology (QIDS), Clinician Rating (QIDS-C), and Self-Report (QIDS-SR): a psychometric evaluation in patients with chronic major depression. *Biol Psychiatry*. 2003;54(5):573–583.
27. Guy W. *ECDEU Assessment Manual for Psychopharmacology, Revised 1976*. Rockville, MD: National Institute of Mental Health, Psychopharmacology Research Branch; 1976:217–222, 313–331.
28. Leon AC, Shea MK, Portera L, et al. Assessing impairment in patients with panic disorder: the Sheehan Disability Scale. *Soc Psychiatry Psychiatric Epidemiol*. 1992;27(2):78–82.
29. Sheehan DV. *The Anxiety Disease*. New York, NY: Edited by Charles ScribnerÇs Sons; 1983.
30. Kind P. The EuroQoL instrument: An index of HRQOL. In: Spilker B, ed. *Quality of Life and Pharmacoeconomics in Clinical Trials*. 2nd ed. Philadelphia, PA: Lippincott-Raven; 1996:191–201.
31. Trivedi MH, Rush AJ, Wisniewski SR. Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: implications for clinical practice. *Am J Psychiatry*. 2006;163(1):28–40.
32. Wade AG, Schlaepfer TE, Andersen HF, et al. Clinical milestones predict symptom remission over 6-month and choice of treatment of patients with major depressive disorder (MDD). *J Psychiatr Res*. 2009;43(5):568–575.
33. Ciudad A, Álvarez E, Roca M, et al. Early response and early remission as predictors of good outcome of a depressive episode. *J Clin Psychiatry*. 2012;73(2):185–191.
34. Judd LL. The clinical course of unipolar major depressive disorders. *Arch Gen Psychiatry*. 1997;54(11):989–991.
35. Keller MB. Past, present, and future directions for defining optimal treatment outcome in depression: remission and beyond. *JAMA*. 2003;289(23):3152–3160.
36. Paykel ES, Ramana R, Cooper Z, et al. Residual symptoms after partial remission: an important outcome in depression. *Psychol Med*. 1995;25(6):1171–1180.
37. Romera I, Perez V, Menchón JM, et al. Social and occupational functioning impairment in patients in partial versus complete remission of a major depressive disorder episode. A six-month prospective epidemiological study. *Eur Psychiatry*. 2010;25(1):58–65.
38. Rush AJ, Kraemer HC, Sackeim HA, et al. Report by the ACNP Task Force on response and remission in major depressive disorder. *Neuropsychopharmacology*. 2006;31(9):1841–1853.
39. Nemeroff CB, Entsuah R, Benattia I, et al. Comprehensive analysis of remission (COMPARE) with venlafaxine versus SSRIs. *Biol Psychiatry*. 2008;63(4):424–434.
40. Thase ME, Entsuah AR, Rudolph RL. Remission rates during treatment with venlafaxine or selective serotonin reuptake inhibitors. *Br J Psychiatry*. 2001;178:234–241.
41. Thase ME, Pritchett YL, Ossanna MJ, et al. Efficacy of duloxetine and selective serotonin reuptake inhibitors: comparisons as assessed by remission rates in patients with major depressive disorder. *J Clin Psychopharmacol*. 2007;27(6):672–676.
42. Bech P, Tanghøj P, Cialdella P, et al. Escitalopram dose-response revisited: an alternative psychometric approach to evaluate clinical effects of escitalopram compared to citalopram and placebo in patients with major depression. *Int J Neuropsychopharmacol*. 2004;7(3):283–290.
43. Baldwin DS, Stein DJ, Dolberg OT, et al. How long should a trial of escitalopram treatment be in patients with major depressive disorder, generalized anxiety disorder or social anxiety disorder? An exploration of the randomised controlled trial database. *Hum Psychopharmacol*. 2009;24(4):269–275.

Journal of Affective Disorders 143 (2012) 47–55

Contents lists available at SciVerse ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Research report

Early vs. conventional switching of antidepressants in patients with MDD and moderate to severe pain: A double-blind randomized study

Irene Romera [a,b,*], Victor Pérez [c], Jose Manuel Menchón [d], Alexander Schacht [e], Rita Papen [e], Doris Neuhauser [f], Mocrane Abbar [g], Hernan Picard [h], Inmaculada Gilaberte [i]

[a] Eli Lilly and Company, Madrid 28108, Spain
[b] Universidad Autonoma de Barcelona, Departamento de Psiquiatría, Barcelona, Spain
[c] Hospital de Sant Pau i de la Santa Creu. UAB, CIBERSAM, Barcelona, Spain
[d] Hospital Universitari de Bellvitge. CIBERSAM, Hospitalet de Llobregat, Barcelona, Spain
[e] Eli Lilly and Company, Bad Homburg, Germany
[f] Eli Lilly and Company, Vienna, Austria
[g] Hôspital Carémeau, Nîmes, France
[h] Unité Inserm UMR S894, Saint-Anne hospital, Paris, France
[i] Eli Lilly and Company, Madrid 28108, Spain

ARTICLE INFO

Article history:
Received 24 February 2012
Received in revised form
17 May 2012
Accepted 17 May 2012
Available online 1 August 2012

Keywords:
Major depressive disorder
Early switch strategy
Antidepressant switch
Treatment optimization
Painful physical symptoms

ABSTRACT

Background: Concomitant painful physical symptoms in depressive patients frequently impair functioning and failure to treat these symptoms may adversely impact treatment outcomes of depression. Early vs. conventional switch of antidepressants were compared in patients with major depressive disorder (MDD) and moderate to severe pain.

Method: Pre-specified subgroup analysis of a 16-week, randomized, double-blind clinical study on MDD patients with >30 mm overall pain visual analog scale (VAS). Patients not achieving 30% reduction Hamilton Depression Rating Scale (HAM-D) after 4 weeks escitalopram (10 mg/day) were randomized to duloxetine 60–120 mg/day (*early switch*) or continued on escitalopram (*conventional switch*) with non-responders at week 8 switching to duloxetine. Endpoints were time to confirmed response and remission, VAS pain severity, and Sheehan disability scale (SDS). Switch strategies were compared using Kaplan–Meier, logistic regression, and repeated measures analyses.

Results: No differences between early and conventional switching were found in time to confirmed response after randomization (3.9 vs. 4.1 weeks, $p=0.511$) or remission (6.0 vs. 8.0 weeks, $p=0.238$). Significantly lower VAS mean pain levels at for overall pain, headache, back pain, shoulder pain, interference with daily activities, and time being awake in pain were found for patients in the early switching group. Time to achieving normal functioning (SDS total score <6) was shorter in the early switching group ($p=0.042$). Safety results were comparable between switch strategies.

Conclusions: In MDD patients with moderate to severe painful physical symptoms not improving after 4 weeks of treatment with escitalopram, an earlier switch to duloxetine may lead to better pain and functional outcomes.

1. Introduction

Major depressive disorder (MDD) is often accompanied by painful physical symptoms (PPS) (Bair et al., 2003, 2004; Fava et al., 2004; Simon et al., 1999; Axford et al., 2008; Kroenke et al., 2008). PPS are not only reported by the majority of patients with MDD (Bair et al., 2003) but are frequently the only presenting symptoms in MDD patients expressing complaints to their general practitioner (69% according to Simon et al., 1999). PPS are experienced by many MDD patients as being of moderate to severe intensity and may also impact further aspects of the patients' life such as general well-being, functioning, disability and participation in social life, and are predictors for poor treatment outcome in depression (Fava et al., 2004; Gameroff and Olfson, 2006; Leuchter et al., 2010).

Switching to another antidepressant is a commonly used strategy in patients with selective serotonin reuptake inhibitor (SSRI) treatment failure (Fava et al., 2003; Fava, 2010; Hirschfeld, 2002; Nierenberg et al., 2003; Papakostas et al., 2008; Perahia et al., 2008; Rush et al., 2006; Thase et al., 2000). However, although the general approach of switching antidepressant treatment in case of non-response is commonly accepted, there is a lack of studies guiding the clinician on how to conduct that

* Corresponding author at: Clinical Research Physician Neuroscience, Medical Department, Eli Lilly Spain SA, Avenida de la Industria, 30, 28108 – Alcobendas, Madrid 28108, Spain. Tel.: +34 916233632.
E-mail address: romera_irene@lilly.com (I. Romera).

0165-0327/$ - see front matter © 2012 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.jad.2012.05.024

change. More specifically, there is a lack of data about the best time point for initiating a switch. It is generally believed that the clinical onset of antidepressant activity is delayed (Quitkin et al., 1996) and consequently, a "watchful waiting approach" is often adopted before switching antidepressants is considered leading to treatment switches in non-responders after 6 to 12 weeks (Anderson et al., 2000).

Consequently, current treatment guidelines suggest a prolonged period of initial treatment with antidepressants to determine how much a patient will benefit from treatment (Fochtmann and Gelenberg, 2005) and a recent key study to assess usefulness of switching antidepressant treatments (STAR*D) had the first change from initial treatment scheduled only after 14 weeks (Leuchter et al., 2010). However, a number of studies found that a small but early improvement of $\geq$20% in the first 2 weeks of treatment is a good predictor of sustained response (Nierenberg et al., 1995, 2000; Szegedi et al., 2003, 2009). Accordingly, lack of early improvement has been found to be a strong predictor of clinical non-response in depressive patients (Szegedi et al., 2009). More specifically, patients not experiencing an onset of response (defined as a score reduction on the HAM-D of $<$30%) by week 4 had a high chance of not exhibiting response by the end of the trial (Szegedi et al., 2003; Nierenberg et al., 2000).

Based on this, a recent NICE assessment concluded that 3 to 4 weeks can be considered a reasonable time to initiate change of initial treatment in patients who did not improve their depressive symptoms yet (National Institute of Healthy and Clinical Excellence (NICE), 2010). Recently we (Romera et al. 2012) conducted a randomized clinical trial comparing an early switch (after 4 weeks) based on improvement criteria ($\geq$30%) with a conventional switch (after 8 weeks) based on treatment response ($\geq$50% improvement in the Hamilton Depression Scale [HAM-D]) from an SSRI (i.e., escitalopram) to a serotonine-noradrenaline reuptake inhibitor (SNRI, i.e., duloxetine). According to a pre-specified subgroup analysis, the present publication presents the results for MDD patients with moderate to severe PPS.

An early improvement and sustained response to MDD treatment is of particular importance in patients with moderate to severe PPS because these patients have on average more serious disease and are additionally impaired by their pain and consequently have poorer treatment outcomes (Fava et al., 2004; Leuchter et al., 2010). Duloxetine, which has proven direct efficacy on pain (Lunn et al., 2009) was used as second line medication in this study.

Therefore, the analysis of the subgroup of patients with moderate to severe pain is of particular interest to assess the impact of different switching strategies from an SSRI to an antidepressant with proven efficacy on PPS on patient outcomes.

We tested the hypotheses that in MDD patients with moderate to severe PPS, who did not improve by $\geq$30% after 4 weeks of treatment with escitalopram according to the HAM-D, would benefit from an early switch of treatment to duloxetine, when compared to the conventional switching approach, where the decision about medication switching was taken only after 8 weeks if patients were still HAM-D non-responders ($<$50% improvement) at that time point. This was assessed by testing for significant differences in HAM-D, pain symptoms, and functional outcomes between the early switching and the conventional switching group after 8, 12, and 16 weeks of treatment.

2. Methods

This manuscript presents results of a protocol-defined subgroup analysis of patients with moderate to severe PPS based on a randomized controlled trial in patients with MDD performed at 60 centers in 11 European countries. The overall results of this study have already been published (Romera et al., 2012) and the study was conducted according to good clinical practice and was approved by the institutional review boards at each center. Written informed consent was obtained from all patients before conducting any study procedures. We present the study design features relevant to the subgroup analysis of patients with moderate to severe PPS at baseline. Further details of the general study methodology have been reported in Romera et al. (2012).

2.1. Patients and study design

Male or female outpatients aged $\geq$18 years who met the diagnostic criteria for single or recurrent episodes of MDD according to the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition(DSM-IV®–TR) (American Psychiatric Association, 1994) were enrolled. For a detailed list of exclusion criteria at baseline see Romera et al. (2012).

Starting at baseline, all patients were treated with 10 mg/day escitalopram for 4 weeks (Study Period I). Patients with an improvement in psychiatric symptoms at week 4 (i.e., $\geq$30% reduction in baseline score of the HAM-D) were withdrawn from the study and continued treatment according to clinical practice. The selection of $<$30% improvement in the HAM-D after 4 weeks of treatment, as a criterion for non-response, was based on previous post-hoc analyses from clinical studies (Nierenberg et al., 2000; Szegedi et al., 2003). All patients not improving were randomized 1:1 to double-blind continuation treatment according to a pre-defined early or conventional switch strategy (Study Period II [SPII]), no stratification for baseline pain severity was performed.

Patients in the **early switch strategy** arm received a flexible dose of duloxetine (60–120 mg/day) during weeks 4 to 16. In the **conventional switch strategy** arm, patients continued to take escitalopram (flexible dose; 10–20 mg/day) during weeks 4 to 8 and were reassessed for treatment response at week 8. At that time, non-responders (i.e., $<$50% HAM-D score reduction from baseline) were switched to duloxetine (60–120 mg/day) from week 8 to 16, while responders continued on escitalopram (10–20 mg/day) from week 8 to 16. Patients who completed 16 week treatment or those who discontinued the study prematurely after randomization could enter an optional 2-week double-blind tapering phase (Study Period III). Patients who achieved confirmed remission before week 16 were allowed to leave the study and were considered to have completed the study.

For this pre-specified subgroup analysis, only patients who reported moderate to severe pain according to the visual analog scale (VAS) overall pain score ($>$30 mm) at baseline were included. Pain symptoms were not used for the classification of symptom improvement at week 4 or response assessments at weeks 8 or 12.

2.2. Measures

Efficacy measures analyzed for symptoms of depression were the HAM-D total score based on the 17 question version of the scale (Hamilton, 1960, 1967). In addition to standard analyses of HAM-D scores over time, HAM-D scores were utilized to analyze the time to confirmed response and time to confirmed remission. For functional outcomes assessment the Sheehan Disability Scale (SDS; Sheehan, 1983) was used. Normal functioning was defined as a SDS total score of $\leq$6 (Sheehan and Sheehan, 2008). For the assessment of pain during the past week, 100 mm VAS were used referring to: overall pain, headache, back pain, shoulder pain, pain interference with daily activities (including work, school,

housework, recreational, social, and family activities), and time in pain while awake.

Study measures were collected by the investigators. HAM-D and pain VAS were collected at baseline (week 0), at week 4 (randomization), and every 2 weeks thereafter until week 16. Telephone-based structured interviews (Trivedi et al., 2006) based on the HAM-D were performed by the investigators at weeks 5, 7, 9, 11, 13, and 15 and subsequent site based HAM-D assessments were performed to capture the time of confirmed response or confirmed remission as accurately as possible. Functioning data (SDS) were collected at weeks 0, 4, 8, 12, and 16. Confirmed response was defined as $\geq$50% HAM-D reduction in 2 consecutive weekly visits. Confirmed remission was defined as a HAM-D total score of $\leq$7 maintained for at least 2 consecutive weekly visits.

Spontaneously reported adverse events (AEs), vital signs, and concomitant medication were recorded at each visit and are displayed descriptively by switching approach.

2.3. Statistical analysis

The primary hypotheses of superiority of the early switch strategy vs. the conventional switch strategy in the overall sample was based on time to confirmed response and time to confirmed remission and is published elsewhere (Romera et al. 2012). All analyses within this report relate to the pre-specified secondary objective and use a 2-sided significance level of 0.05 with no further adjustment for multiplicity.

The time to HAM-D based confirmed response or remission and the time to SDS normal functioning were analyzed using Kaplan–Meier-plots (KM plots). The respective proportions reported are also based on the KM plots. Generalized Wilcoxon tests were used to compare switch strategies for time to response analyses. Proportions were compared using the formula for asymptotic normality following the central limit theorem.

Statistical methods to analyze secondary outcomes included mixed models for repeated measures (MMRM) analyses on the different questionnaires and VAS. The models included terms for switch strategy, country, visit, strategy-by-visit interaction, baseline score, and baseline-by-visit interaction. The covariance structure converging to the best fit for the analysis of the variable, as determined by Akaike's information criterion, was used in the model for all efficacy variables. Analyses of covariance (ANCOVA) with terms for switch strategy, country and, as applicable, the baseline score of the dependent variable were performed for the SDS total and item scores using the last-observation-carried-forward approach.

Proportions of patients with AEs, serious adverse events (SAEs), and AEs leading to discontinuation were presented by switch strategy for the randomization period including the discontinuation period and were compared using Fisher's exact test. Vital signs were summarized descriptively.

The data analysis was generated using SAS software version 8.2 or higher (Copyright, SAS Institute Inc.; SAS and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institute Inc., Cary, NC, USA).

3. Results

3.1. Disposition of patients

See Fig. 1 for a flow chart of patient disposition during the study. Initially 877 patients were screened at study entry and 434 (49.5%) patients had moderate to severe pain ($>$30 mm VAS overall pain score) started study treatment with escitalopram 10 mg/day. After 4 weeks, 291 patients (67.1%) did not achieve improvement (i.e., a reduction from baseline of $\geq$30% in the HAM-D total score) and were randomized. Of those, 138 patients were treated according to the early switch strategy and 153 patients according to the conventional switch strategy. Of the patients in the conventional switch strategy, 89 (62.2%) did not achieve response at week 8 and were switched to duloxetine. The number of discontinuations during Study Period II was similar for both strategies (early switch: 24.6%; conventional switch: 24.8%).

3.2. Demographic and clinical characteristics

Patient demographics and baseline disease characteristics are summarized in Table 1. The results of the baseline total scores for HAM-D and SDS indicated that patients suffered from moderate to severe MDD. A chronic course ($>$6 months) of the current depressive episode was reported for 21.3% of the patients. For the patients included in this analysis, mean pain at baseline was 60 mm for the overall pain VAS.

Before study entry, 39.5% of patients were on antidepressant treatment; frequencies were balanced between switching groups, with most commonly reported previous antidepressants being SSRIs (37.1% of patients overall).

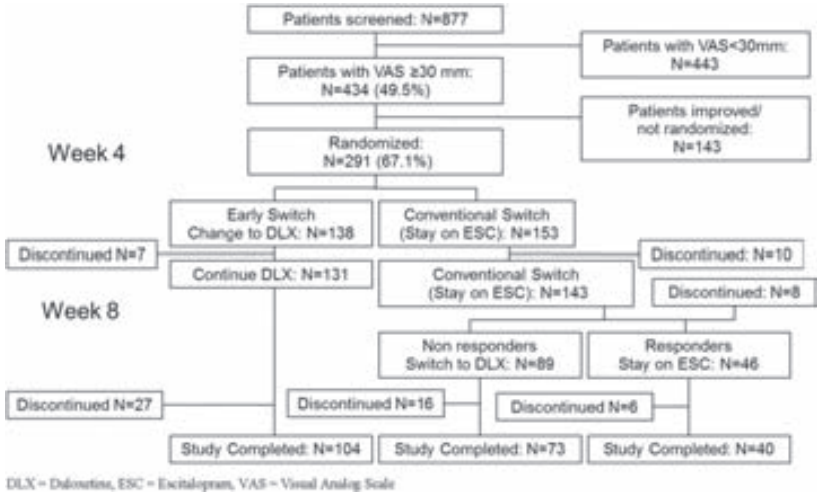


Fig. 1. Patient disposition. DLX=duloxetine, ESC=escitalopram, VAS=Visual analog scale.

Table 1
Baseline demographics and clinical characteristics.

	Early switch strategy ($N=138$)	Conventional switch strategy ($N=153$)
Age (years)		
Mean (SD)	49.0(12.63)	48.5(11.67)
Median (range)	49.9(19.7/76.2)	48.8(19.2/72.3)
Gender (n [%])		
Female	108(78.3)	114(74.5)
Male	30(21.7)	39(25.5)
Race (n[%])		
Black or African American	2(1.4)	1(0.7)
Caucasian	136(98.6)	152(99.3)
Number (%) of patients with at least 1 previous episode	119(86.2)	117(76.5)
Number of previous episodes or exacerbations		
Mean (SD)	3(3.21)	2.4(2.41)
Median (Q1/Q3)	2(1/4)	2(1/4)
Time since the first episode (years)		
Mean (SD)	11.2(11.85)	9.5(10.46)
Median (Q1/Q3)	8.7(2.3/16.6)	6.2(0.8/14.6)
Number (%) of patients with current episode >6 months	36(26.1)	26(17.0)
HAM-D total score		
Mean (SD)	24.6(3.25)	25.0(3.74)
Median (Q1/Q3)	24(23/27)	25(22/27)
VAS overall pain [mm]		
Mean (SD)	60(18.5)	59 (18.1)
Median (Q1/Q3)	56 (45/75)	59(44/74)
SDS total score		
Mean (SD)	20.9(5.26)	20.6(5.71)
Median (Q1/Q3)	21(19/24)	22(18/24)

At randomization (week 4), the overall mean HAM-D total score was 22.2. The VAS mean values of overall pain were 48 mm for all patients.

3.3. HAM-D response and remission

The proportion of patients achieving a HAM-D based confirmed response or remission at the end of SPII (16 weeks) was comparable between switching groups. HAM-D response was confirmed in 61.6% of the early switch and 64.1% of the conventional switching group ($p=0.652$) and the respective percentages for confirmed remission were 35.5% for the early and 32.7% for the conventional switching groups ($p=0.840$). No statistically significant differences (Wilcoxon test) in time to confirmed response ($p=0.511$) or time to confirmed remission ($p=0.238$) were found between switching groups (see Fig. 2).

The time at which 25% of patients had reached a confirmed response after randomization was 3.9 weeks in patients randomized to the early switching group and 4.1 weeks in those randomized to the conventional switching group. For confirmed remission the corresponding values were 6.0 weeks after randomization for the early and 8.0 weeks for the conventional switching group. The median (50% of patients) time to confirmed response was 7.0 weeks after randomization in both switching groups. The median time to confirmed remission could not be estimated due to the low percentage of patients achieving confirmed remission.

3.4. VAS pain scales

Significantly higher VAS mean pain levels at week 6 and/or week 8 (i.e., 2 and 4 weeks after randomization) were measured for overall pain, headache, back pain, shoulder pain, interference with daily activities, and time being awake in pain for patients in the conventional switching group (Table 2). VAS pain level results were no longer statistically significantly different between switching groups at the end of the study (week 16).

3.5. Sheehan disability scale (SDS)

Patient disability as measured by the SDS total score did not improve statistically significantly different between the switching groups when analyzed as a continuous variable with the MMRM approach. SDS total score at week 16 was 10.36 (95% confidence interval [CI]: 8.23; 12.50) in the early switching group and 10.68 (95% CI: 8.62; 12.73) in the conventional switching group (difference -0.31; 95% CI: -2.87; 2.24; $p=0.809$). However, when analyzed as a categorical variable (achieving normal functioning, i.e., an SDS total score <6) the time to SDS normal functioning analysis revealed that patients in the early switching group achieved normal functioning earlier than patients in the conventional switching group ($p=0.042$). In addition, the categorical analysis regarding the proportion of patients achieving normal functioning showed statistically significantly higher proportions of patients with normal functioning in the early switching group compared to the conventional switching group at all points in time measured (week 8, 12, and 16; see Fig. 3).

3.6. Safety and tolerability findings

During week 4 to 16 when treatments differed between switching groups, 41.3% of patients in the early switching group and 35.9% in the conventional switching group reported at least 1 adverse event (AE). 2.9% of the patients in in the early and 2.0% of those in the conventional switching group discontinued the study due to an AE (Table 3A). AEs occurring in $\geq 4\%$ of patients in any strategy arm were headache, nausea, and hyperhidrosis. No statistically significant differences in the proportion of patients experiencing a specific preferred term or in the overall proportion of patients experiencing any AE were found between switching groups (Table 3B). No relevant findings were seen for vital signs.

4. Discussion

The present analysis was based on the HMGD study evaluating MDD patients treated with 10 mg/day escitalopram for 4 weeks and not achieving at least 30% reduction in their depressive symptomatology as measured by the HAM-D (Romera et al., 2012) and included all patients with moderate to severe pain (overall pain VAS >30 mm) at baseline. At week 4 patients were randomized to early and conventional switching strategies to duloxetine. For depressive symptoms, no statistically significant differences in core psychiatric symptoms measured by the HAM-D scale were found by analyzing confirmed response and remission following randomization. Statistically significantly lower pain levels were found in the early switching group at week 6 and 8 (i.e., 2 and 4 weeks after randomization) for most VAS pain scales but were not sustained at weeks 12 and 16 (i.e., 8 and 12 weeks after randomization). A categorical analysis of the proportion of patients achieving functional remission showed a significantly higher proportion of remitted patients in the early switching group at weeks 8, 12, and 16. Safety and tolerability were similar between both switching groups.

When comparing these results with the primary analysis based on all 638 patients of the HMGD study (Romera et al., 2012), differences in the HAMD remission rates were statistically significant, which we did not find in the present subgroup analysis of patients with moderate to severe pain at baseline.

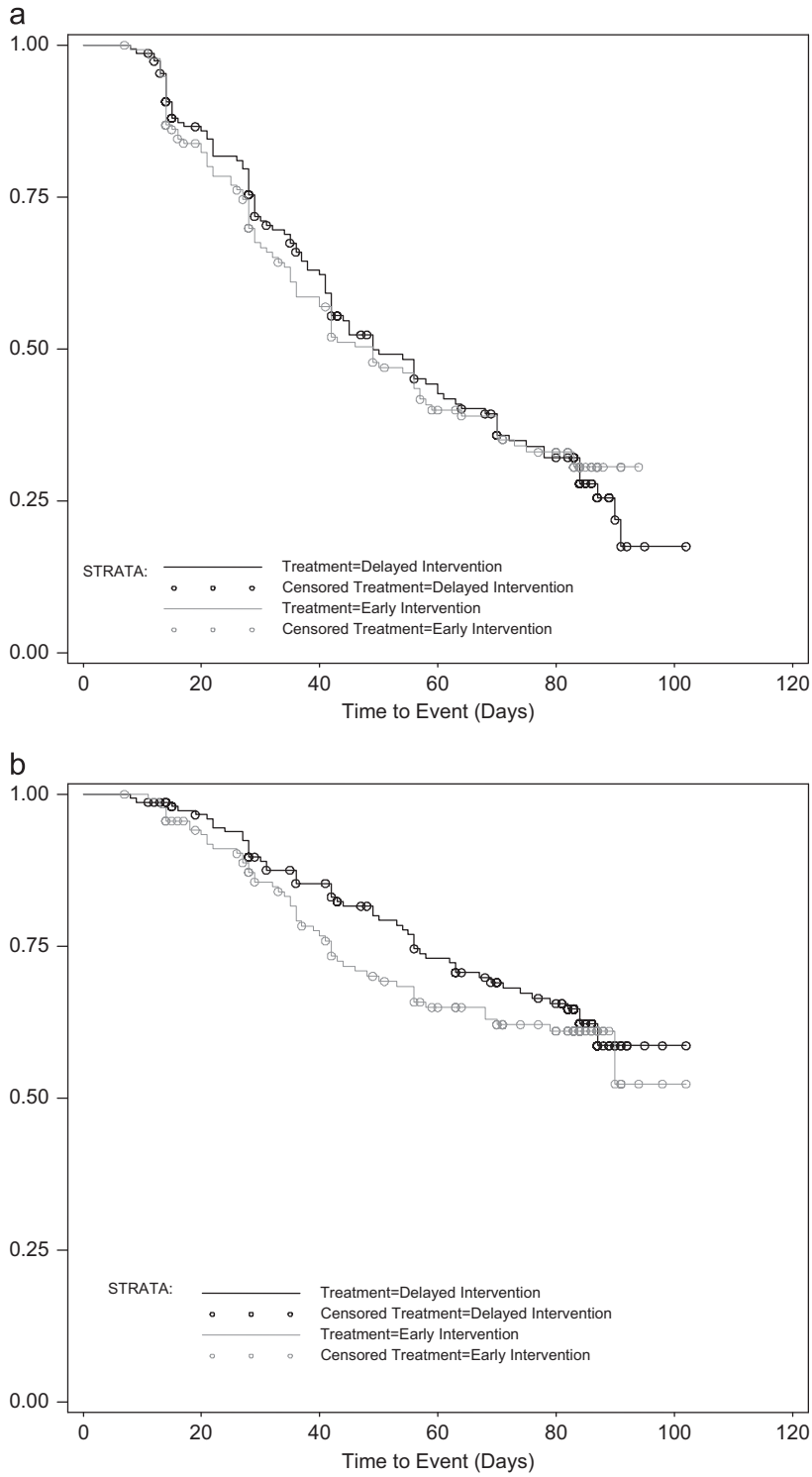


Fig. 2. Kaplan–Meier plots of HAM-D confirmed response (a) and confirmed remission (b) after randomization at week 4.

This may be explained by the reduced number of patients in our analysis and the fact that already in the full study population the difference was only moderate.

The early improvement in the VAS pain measures seen in early switching group is in accordance with duloxetine data showing pain improvement already after the first or second week of treatment (Hirschfeld et al., 2005; Sagman et al., 2011). However, in our study, differences are lost later, probably because 65% of the patients in the conventional switching group were treated with duloxetine from week 8 (i.e., 4 weeks after randomization), therefore reducing differences in antidepressant treatment between switching groups. A fast adjustment of pain symptoms after treatment switches in depressive treatments has been shown also in other studies (Perahia et al., 2009; Sagman et al., 2011).

In this study duloxetine was used as a second line treatment however, due to its efficacy on pain symptoms, it could be

Table 2
VAS pain scores—Mixed models for repeated measures analysis.

Visit	Early switch strategy (*N*=138)		Conventional switch strategy (*N*=153)		Difference between LS means		
	LS mean	95% CI	LS mean	95% CI	Estimate	95% CI	*p*-value [a]
Overall pain [mm]							
Week 4[b]	45	(23.4)	50	(26.3)	–	–	–
Week 6	**37.8**	**32.3; 43.2**	**47.1**	**41.9; 52.4**	**−9.4**	**−15.4; −3.3**	**0.002**
Week 8	**33.8**	**28.2; 39.3**	**41.1**	**35.7; 46.5**	**−7.3**	**−13.6; −1.1**	**0.021**
Week 10	33.3	27.6; 38.9	36.2	30.7; 41.7	−2.9	−9.4; 3.6	0.378
Week 12	29.8	23.9; 35.7	35.4	29.8; 41.1	−5.6	−12.4; 1.2	0.106
Week 14	25.9	19.8; 32.0	31.7	25.9; 37.6	−5.8	−13.0; 1.4	0.112
Week 16	25.2	19.0; 31.3	30.4	24.5; 36.3	−5.2	−12.5; 2.1	0.162
Headache [mm]							
Week 4[b]	35	(26.7)	39	(29.1)	–	–	–
Week 6	31.4	26.1; 36.6	36.4	31.4; 41.4	−5.0	−11.0; 0.9	0.096
Week 8	**27.8**	**22.5; 33.1**	**34.1**	**29.0; 39.3**	**−6.4**	**−12.5; −0.2**	**0.042**
Week 10	28.8	23.3; 34.3	29.9	24.6; 35.2	−1.1	−7.5; 5.3	0.743
Week 12	25.1	19.3; 30.9	31.5	26.0; 36.9	−6.4	−13.2; 0.4	0.067
Week 14	21.5	15.5; 27.5	25.8	20.1; 31.5	−4.3	−11.5; 2.9	0.239
Week 16	22.6	16.6; 28.7	26.1	20.4; 31.9	−3.5	−10.8; 3.8	0.348
Back pain [mm]							
Week 4[b]	42	(30.1)	42	(29.9)	–	–	–
Week 6	**31.5**	**26.1; 37.0**	**38.2**	**33.1, 43.6**	**−6.8**	**−12.8; −0.7**	**0.028**
Week 8	30.1	24.6; 35.7	34.7	29.3; 40.1	−4.6	−10.8; 1.7	0.153
Week 10	28.0	22.3; 33.7	29.8	24.3; 35.3	−1.8	−8.3; 4.7	0.593
Week 12	27.2	21.3; 33.1	33.3	27.6; 38.9	−6.1	−12.9; 0.8	0.084
Week 14	22.9	16.8; 29.0	28.2	22.3; 34.1	−5.3	−12.6; 1.9	0.149
Week 16	21.6	15.5; 27.8	26.4	20.6; 32.3	−4.8	−12.1; 2.5	0.198
Shoulder pain [mm]							
Week 4[b]	32	(30.9)	35	(31.8)	–	–	–
Week 6	**24.7**	**19.6; 29.9**	**34.9**	**30.0; 39.8**	**−10.2**	**−15.9; −4.4**	**<0.001**
Week 8	**21.4**	**16.2; 26.6**	**31.2**	**26.1; 36.2**	**−9.8**	**−15.7; −3.8**	**0.001**
Week 10	23.9	18.5; 29.2	29.7	24.5; 34.9	−5.8	−12.0; 0.4	0.065
Week 12	**19.9**	**14.3; 25.5**	**28.5**	**23.1; 33.8**	**−8.5**	**−15.1; −2.0**	**0.011**
Week 14	20.9	15.1; 26.7	24.9	19.3; 30.5	−4.0	−11.0; 2.9	0.253
Week 16	16.3	10.4; 22.2	22.9	17.3; 28.5	−6.6	−13.6; 0.5	0.067
Interference with daily activities [mm]							
Week 4[b]	39	(28.2)	45	(30.1)	–	–	–
Week 6	**32.1**	**26.7; 37.6**	**40.1**	**34.9; 45.3**	**−8.0**	**−14.0; −1.9**	**0.010**
Week 8	29.1	23.6; 34.6	34.9	29.5; 40.2	−5.8	−12.0; 0.5	0.070
Week 10	29.0	23.4; 34.6	31.5	26.1; 37.0	−2.5	−9.0; 3.9	0.443
Week 12	25.8	19.9; 31.7	31.0	25.4; 36.6	−5.2	−12.1; 1.6	0.133
Week 14	23.3	17.3; 29.4	28.1	22.3; 33.9	−4.8	−12.0; 2.4	0.191
Week 16	21.7	15.5; 27.8	25.8	19.8; 31.7	−4.1	−11.4; 3.2	0.274
Time in pain when awake [mm]							
Week 4[b]	47	(30.6)	54	(30.3)	–	–	–
Week 6	**36.8**	**31.0; 42.6**	**43.9**	**38.3; 49.5**	**−7.2**	**−13.7; −0.6**	**0.032**
Week 8	**33.6**	**27.7; 39.5**	**41.5**	**35.8; 47.2**	**−7.9**	**−14.6; −1.1**	**0.022**
Week 10	34.0	27.9; 40.0	34.7	28.8; 40.6	−0.8	−7.8; 6.2	0.830
Week 12	**27.9**	**21.6; 34.2**	**36.3**	**30.3; 42.4**	**−8.4**	**−15.8; −1.0**	**0.026**
Week 14	28.5	22.0; 35.1	31.3	25.0; 37.6	−2.8	−10.6; 5.0	0.478
Week 16	29.6	22.9; 36.3	30.2	23.8; 36.5	−0.6	−8.6; 7.4	0.891

CI=confidence interval; LS=least square; N=total number of patients.

[a] *P*-values from mixed model for repeated measures that included terms for strategy, country, visit, strategy-by-visit interaction, baseline score, and baseline-by-visit interaction; $p < 0.05$ highlighted in bold.

[b] Unadjusted values (not MMRM).

considered as an initial option in patients with depression and PPS (Detke et al., 2002).

Of particular relevance is our finding patients in the early switching group achieved a higher proportion of normal levels of functioning and that this difference was still maintained after 16 weeks (i.e., 12 weeks after randomization), when between-group differences in other parameters were no longer statistically significant. The time course of functional improvement and psychiatric and pain symptoms are not necessarily aligned to each other and Sheehan et al. (2011) found that functional improvements measured by the SDS may lag a week behind improvements in pain. This makes it reasonable that by switching to duloxetine early in MDD patients with moderate to severe PPS a normal status of functioning cannot only be achieved earlier than in patients switched later but that this effect is also maintained even after a longer period of time.

This is of particular interest as the optimal treatment outcome of depression is not only remission of psychiatric and/or pain symptoms but also the possibility for the patient to achieve normal functioning (Keller, 2003). Zimmerman stated that from the patient's perspective normal functioning is even more relevant than complete resolution of depressive symptoms (Zimmerman et al., 2006).

Normal levels of functioning have also been linked to lower treatment costs and burdens of the disease for the family and healthcare system, including the ability to work again (Greer

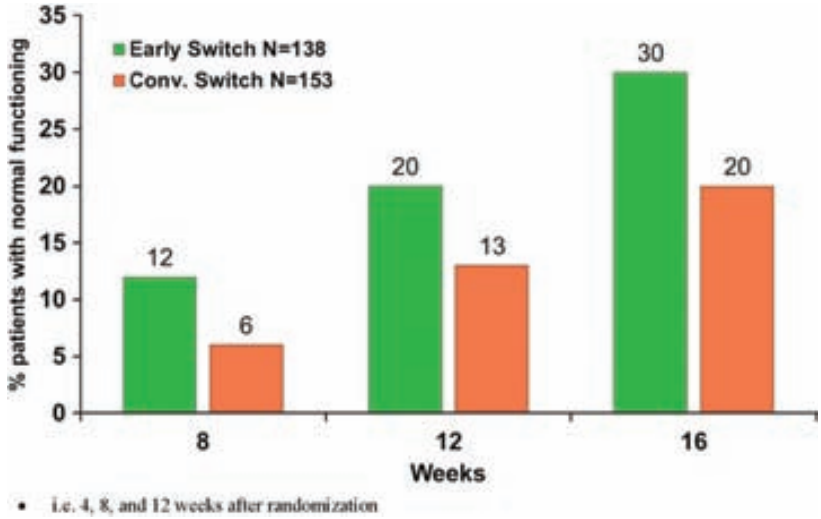


Fig. 3. SDS total score, Kaplan–Meier analysis for time to normal functioning: proportion of patients achieving normal functioning at week 8, 12, and 16*. i.e., 4, 8, and 12 weeks after randomization.

Table 3
A: Overview of Adverse Events; B: Treatment-emergent Adverse Events reported by at least 2% of Patients in either Switch Strategy Group.

A	Number (%) of patients	
Category	**Early switch strategy (*N*=138)**	**Conventional switch strategy (*N*=153)**
At least 1 AE	57 (41.3)	55 (35.9)
At least 1 drug-related AE	37 (26.8)	35 (22.9)
At least 1 SAE	7 (5.1)	2 (1.3)
At least 1 drug-related SAE	2 (1.4)	1 (0.7)
Discontinued due to AE	4 (2.9)	3 (2.0)

B	Number (%) of patients		*p*-value [a]
Category	**Early switch (*N*=138)**	**Conventional switch (*N*=153)**	
Headache	13 (9.4)	21 (13.7)	0.839
Nausea	7 (5.1)	2 (1.3)	0.090
Nasopharyngitis	3 (2.2)	6 (3.9)	0.506
Hyperhidrosis	6 (4.3)	2 (1.3)	0.156
Dizziness	5 (3.6)	3 (2.0)	0.484
Diarrhoea	3 (2.2)	5 (3.3)	0.726
Dry mouth	5 (3.6)	1 (0.7)	0.105
Blood pressure diastolic decreased	4 (2.9)	1 (0.7)	0.194
Hypertension	3 (2.2)	2 (1.3)	0.671
Hot flush	3 (2.2)	0 (0.0)	0.105
Fatigue	0 (0.0)	3 (2.0)	0.249

AE=adverse event; *N*=total number of patients; SAE=serious adverse event.
N=total number of patients; TEAE=treatment-emergent adverse event.
Note: Sorted by frequency in the early intervention arm; includes TEAEs during the taper period at the end of Study Period II for those who did not continue into Study Period III.

[a] *p*-value according to Fisher's exact test.

et al., 2010). In addition long-term treatment outcomes of MDD patients achieving functional remission are favorable and this is of specific importance in the patient with moderate to severe PPS that were analyzed here because of their relative poor outcome prognosis compared to MDD patients with no or mild PPS (Leuchter et al., 2010).

Results from our study are generally in alignment with the preliminary results of a smaller open label study of similar design reported by Nakajima et al. (2011). They reported higher rates of response and remission in the group switching the antidepressant after 2 weeks compared to those continuing on the initial antidepressant.

Limitations of this publication are that this pre-specified subgroup analysis did not involve stratified randomization of patients with moderate to severe PPS at baseline and that the duration of the data collection periods was restricted to 16 weeks. The latter does not allow assessment if the observed improvement in functional remission in patients in the early switching group can be maintained for more than 12 weeks after switching. In addition, our results cannot necessarily be generalized to different patient populations of MDD patients and to switches from initial treatment with other SSRIs or SNRIs to duloxetine or other antidepressants with different modes of action. As no specific washout period was required prior to study entry, 39.5% of the patients were on antidepressant treatment when initiating study treatment. This may introduce a bias, however this naturalistic approach better reflects clinical practice. A structured assessment for the diagnosis of MDD was not used; however, all participating principal

investigators were psychiatrists and the diagnosis was based on DSM-IV criteria.

As has been discussed in the introduction (Fava et al., 2004; Gameroff and Olfson, 2006; Leuchter et al., 2010), a several post-hoc analyses showed that in the case of lack of early improvement, an early switch of treatment instead of a watchful waiting approach could improve the treatment outcomes of depression. This is one of the first studies to evaluate early vs. conventional switching strategies in patients with MDD.

Our results suggest that for the subgroup of MDD patients with concomitant moderate or severe PPS, an early treatment decision to switch to duloxetine in case of early non-improvement with escitalopram could be particularly relevant. These difficult to treat patients might improve pain severity and consequently patient functioning when switched to duloxetine as an antidepressant with direct action on PPS. Additional studies with similar populations of MDD patients and comparable design evaluating early vs. conventional switching strategies are needed to confirm our results.

Role of funding source

The present study has been fully supported by funding from Eli Lilly and Company.

Conflict of interest

Dr. Irene Romera, Dr. Alexander Schacht, Rita Papen, Dr. Hernan Picard and Dr. Inmaculada Gilaberte are full time employees of Eli Lilly. Dr. Irene Romera is also an affiliate with the Universidad Autonoma de Barcelona, Departamento de Psiquiatría.

Dr. Victor Perez has received grant support from Eli Lilly, Lundbeck, Boehringer, Pfizer, Astra Zeneca, and GSK; has received honoraria from Servier, Eli Lilly, BMS-Otsuka, GSK, Astra Zeneca, and Boehringer; has served as a consultant for and/or on advisory boards for Eli Lilly, BMS, and AstraZeneca.

Dr. Jose M Menchón declares that he has received funding from the University of Barcelona, the Bellvitge University Hospital-IDIBELL, and from the Spanish Ministry of Science and Innovation, Instituto de Salud Carlos III, Centro de Investigacion en Red de Salud Mental (CIBERSAM). He has also received honoraria as a consultant from Almirall, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Janssen, Lundbeck, and Wyeth.

Dr. Mocrane Abbar has received honoraria from Pfizer, Roche, Lundbeck, Organon, Jansen, Novartis, Sanofi, Servier, Eli Lilly, BMS-Otsuka, GSK, Sanofi, Astra Zeneca, Boehringer, and Wyeth; has served as a consultant for and/or on advisory boards for Sanofi, Eli Lilly, BMS-Otsuka, GlaxoSmithKline, and AstraZeneca.

Acknowledgement

We thank Maria Isabel Vazquez, Belen Yruretagoyena, Pepa Polavieja, and Deborah Quail from Lilly for their help with the protocol development and study implementation; Dr James Russell, Dr David Perahia, Dr Jesús Hernandez from Eli Lilly and Dr José Antonio Sacristan from Lilly Spain who provided medical advice on the study design (Jesús Hernandez is currently working for the Centro de Investigación Médica Aplicada de la Universidad de Navarra, Spain); Dr. Thomas Wagner of Trilogy Writing & Consulting GmbH (Frankfurt, Germany) who provided medical writing support; and the principal investigators, and the patients for their voluntary participation.

References

American Psychiatric Association, 1994, Practice Guideline for the Treatment of Patients with Major Depressive Disorder, third ed. Available at 〈http://www.psychiatryonline.com/pracGuide/pracGuideChapToc_7.aspx〉.

Anderson, I.M., Nutt, D.J., Deakin, J.F., 2000. Evidence-based guidelines for treating depressive disorders with antidepressants: a revision of the 1993 British Association for Psychopharmacology guidelines. British association for psychopharmacology. Journal of Psychopharmacology 14, 3–20.

Axford, J., Heron, C., Ross, F., Victor, C.R., 2008. Management of knee osteoarthritis in primary care: pain and depression are the major obstacles. Journal of Psychosomatic Research 64, 461–467.

Bair, M.J., Robinson, R.L., Eckert, G.J., Stang, P.E., Croghan, T.W., Kroenke, K., 2004. Impact of pain on depression treatment response in primary care. Psychosomatic Medicine 66, 17–22.

Bair, M.J., Robinson, R.L., Katon, W., Kroenke, K., 2003. Depression and pain comorbidity: a literature review. Archives of Internal Medicine 163, 2433–2445.

Detke, M.J., Lu, Y., Goldstein, D.J., Hayes., J.R., Demitrack, M.A., 2002. Duloxetine, 60 mg once daily, for major depressive disorder: a randomized double-blind placebo-controlled trial. Journal of Clinical Psychiatry 63, 308–315.

Fava, M., 2010. Switching treatments for complicated depression. Journal of Clinical Psychiatry 71 (2), e04.

Fava, M., Papakostas, G.I., Petersen, T., Mahal, Y., Quitkin, F., Stewart, J., McGrath, P., 2003. Switching to bupropion in fluoxetine-resistant major depressive disorder. Annals of Clinical Psychiatry 15, 17–22.

Fava, M., Mallinckrodt, C.H., Detke, M.J., Watkin, J.G., Wohlreich, M.M., 2004. The effect of duloxetine on painful physical symptoms in depressed patients: do improvements in these symptoms result in higher remission rates? Journal of Clinical Psychiatry 65, 521–530.

Fochtmann, L.J., Gelenberg, A.J., 2005. Guideline Watch: Practice guideline for the treatment of patients with major depressive disorder, 2. American Psychiatric Association, Washington, DC.

Gameroff, M.J., Olfson, M., 2006. Major depressive disorder, somatic pain, and health care costs in an urban primary care practice. Journal of Clinical Psychiatry 67, 1232–1239.

Greer, T.L., Kurian, B.T., Trivedi, M.H., 2010. Defining and measuring functional recovery from depression. CNS Drugs 24, 267–284.

Hamilton, M., 1960. A rating scale for depression. Journal of Neurology, Neurosurgery, and Psychiatry 23, 56–62.

Hamilton, M., 1967. Development of a rating scale for primary depressive illness. Br. Journal of Social and Clinical Psychology 6, 278–296.

Hirschfeld, R.M., 2002. The use of mirtazapine in difficult-to-treat patient populations. Human Psychopharmacology 17 (Suppl 1), S33–S36.

Hirschfeld, R.M., Mallinckrodt, C., Lee, T.C., Detke, M.J., 2005. Time course of depression-symptom improvement during treatment with duloxetine. Depression and Anxiety 21, 170–177.

Keller, M.B., 2003. Past, present, and future directions for defining optimal treatment outcome in depression: remission and beyond. Journal of the American Medical Association 18, 3152–3160.

Kroenke, K., Shen, J., Oxman, T.E., Williams Jr., J.W., Dietrich, A.J., 2008. Impact of pain on the outcomes of depression treatment: results from the RESPECT trial. Pain 134, 209–215.

Leuchter, A.F., Husain, M.M., Cook, I.A., Trivedi, M.H., Wisniewski, S.R., Gilmer, W.S., Luther, J.F., Fava, M., Rush, A.J., 2010. Painful physical symptoms and treatment outcome in major depressive disorder: a STAR*D (Sequenced Treatment Alternatives to Relieve Depression) report. Psychological Medicine 40, 239–251.

Lunn, M.P., Hughes, R.A., Wiffen, P.J., 2009. Duloxetine for treating painful neuropathy or chronic pain. Cochrane Database of Systematic Reviews, Oct 7:CD007115.

Nakajima, S., Uchida, H., Suzuki, T., Watanabe, K., Hirano, J., Yagihashi, T., Takeuchi, H., Abe, T., Kashima, H., Mimura, M., 2011. Is switching antidepressants following early nonresponse more beneficial in acute-phase treatment of depression: a randomized open-label trial. Progress in Neuro-Psychopharmacology and Biological Psychiatry 35, 1983–1989.

National Institute of Healthy and Clinical Excellence (NICE), 2010, The Treatment and Management of Depression in Adults, in The British Psychological Society & The Royal College of Psychiatrists. Available from: 〈http://www.nice.org.uk/nicemedia/live/12329/45896/45896.pdf〉.

Nierenberg, A.A., McLean, N.E., Alpert, J.E., Worthington, J.J., Rosenbaum, J.F., Fava, M., 1995. Early nonresponse to fluoxetine as a predictor of poor 8-week outcome. American Journal of Psychiatry 152, 1500–1503.

Nierenberg, A.A., Farabaugh, A.H., Alpert, J.E., Gordon, J., Worthington, J.J., Rosenbaum, J.F., Fava, M., 2000. Timing of onset of antidepressant response with fluoxetine treatment. American Journal of Psychiatry 157, 1423–1428.

Nierenberg, A.A., Papakostas, G.I., Petersen, T., Kelly, K.E., Iacoviello, B.M., Worthington, J.J., Tedlow, J., Alpert, J.E., Fava, M., 2003. Nortriptyline for treatment-resistant depression. Journal of Clinical Psychiatry. 64, 35–39.

Papakostas, G.I., Fava, M., Thase, M.E., 2008. Treatment of SSRI-resistant depression: a meta-analysis comparing within-versus across-class switches. Biological Psychiatry 637, 699–704.

Perahia, D.G., Quail, D., Desaiah, D., Corruble, E., Fava, M., 2008. Switching to duloxetine from selective serotonin reuptake inhibitor antidepressants: a multicenter trial comparing 2 switching techniques. Journal of Clinical Psychiatry. 69, 95–105.

Perahia, D.G., Quail, D., Desaiah, D., Montejo, A.L., Schatzberg, A.F., 2009. Switching to duloxetine in selective serotonin reuptake inhibitor non- and partial-responders: effects on painful physical symptoms of depression. Journal of Psychiatric Research 43, 512–518.

Quitkin, F.M., McGrath, P.J., Stewart, J.W., Ocepek-Welikson, K., Taylor, B.P., Nunes, E., Deliyannides, D., Agosti, V., Donovan, S.J., Petkova, E., Klein, D.F., 1996. Chronological Milestones to Guide Drug Change: When Should Clinicians Switch Antidepressants? Archives of General Psychiatry 53, 785–792.

Romera, I., Pérez, V., Menchón, J.M., Schacht, A., Papen, R., Neuhauser, D., Abbar, M., Svanborg, P., Gilaberte, I., 2012. Early switch strategy in patients with major depressive disorder: a double-blind randomized study. Journal of Clinical Psychiatry., 2012.

Rush, A.J., Trivedi, M.H., Wisniewski, S.R., Stewart, J.W., Nierenberg, A.A., Thase, M.E., Ritz, L., Biggs, M.M., Warden, D., Luther, J.F., Shores-Wilson, K., Niederehe, G., Fava, M., 2006. STAR*D Study Team Bupropion-SR, sertraline, or venlafaxine-XR after failure of SSRIs for depression. New England Journal of Medicine 354, 1231–1242.

Sagman, D., McIntosh, D., Lee, M.S., Li, H., Ruschel, S., Hussain, N., Granger, R.E., Lee, A.C., Raskin, J., 2011. Attributes of response in depressed patients switched to treatment with duloxetine. International Journal of Clinical Practice 65, 73–81.
Sheehan, D.V., 1983. The Anxiety Disease. Charles Scribner's Sons, New York, NY.
Sheehan, K.H., Sheehan, D.V., 2008. Assessing treatment effects in clinical trials with the Discan metric of the Sheehan Disability Scale. International Clinical Psychopharmacology 23, 70–83.
Sheehan, D.V., Chokka, P.R., Granger, R.E., Walton, R.J., Raskin, J., Sagman, D., 2011. Clinical and functional outcomes in patients with major depressive disorder and painful physical symptoms switched to treatment with duloxetine. Human Psychopharmacology http://dx.doi.org/10.1002/hup.1199.
Simon, G.E., von Korff, M., Piccinelli, M., Fullerton, C., Ormel, J., 1999. An international study of the relation between somatic symptoms and depression. New England Journal of Medicine 341, 1328–1335.
Szegedi, A., Müller, M.J., Anghelescu, I., Klawe, C., Kohnen, R., Benkert, O., 2003. Early improvement under mirtazapine and paroxetine predicts later stable response and remission with high sensitivity in patients with major depression. Journal of Clinical Psychiatry. 64, 413–420.
Szegedi, A., Jansen, W.T., van Willigenburg, A.P., van der Meulen, E., Stassen, H.H., Thase, M.E., 2009. Early improvement in the first 2 weeks as a predictor of treatment outcome in patients with major depressive disorder: a meta-analysis including 6562 patients. Journal of Clinical Psychiatry. 70, 344–353.
Thase, M.E., Friedman, E.S., Howland, R.H., 2000. Venlafaxine and treatment-resistant depression. Depression and Anxiety 12 (Suppl 1), 55–62.
Trivedi, M.H., Fava, M., Wisniewski, S.R., Thase, M.E., Quitkin, F., Warden, D., Ritz, L., Nierenberg, A.A., Lebowitz, B.D., Biggs, M.M., Luther, J.F., Shores-Wilson, K., Rush, A.J., 2006. STAR*D Study Team medication augmentation after the failure of SSRIs for depression. New England Journal of Medicine. 354, 1243–1252.
Zimmerman, M., Posternak, M.A., McGlinchey, J., Friedman, M., Attiullah, N., Boerescu, D., 2006. Validity of a self-report depression symptom scale for identifying remission in depressed outpatients. Comprehensive Psychiatry 47, 185–188.