

Señor Director

DIRECCION DE NUEVAS CREACIONES

Superintendencia de Industria y Comercio

E. S. D.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 13-035030- -00007-0000

Fecha: 2013-12-04 16:27:52 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 449 RESPUESOPOSICI Folios: 34

Trámite : 011 Evento : 378 Actuación : 449

Referencia : Expediente No. **13.035.030**
Asunto : Solicitud de patente para: **USOS TERAPÉUTICOS DE 1-[2,4-DIMETIL-FENILSULFANIL]FENIL]PIPERAZINA**
Solicitante : **H. LUNDBECK A/S**
Opositor : **LABORATORIO FRANCO COLOMBIANO LAFRANCOL S.A.S.**

I. ALEGATOS CONTESTACIÓN OPOSICIÓN

1. Yo, Luz Clemencia de PAÉZ, en mi condición de apoderada de la sociedad solicitante **H. LUNDBECK A/S**, por el presente escrito doy respuesta a la oposición formulada por la compañía **LABORATORIO FRANCO COLOMBIANO LAFRANCOL S.A.S.** en contra de la solicitud de patente de invención que se tramita en el presente expediente.

II. CONTESTACIÓN DENTRO DEL TÉRMINO LEGAL

El Oficio No. **16702**, mediante el cual su Despacho admitió a trámite la oposición presentada por **LABORATORIO FRANCO COLOMBIANO LAFRANCOL S.A.S.** y dispuso otorgar a mi representada término para presentar sus argumentaciones a favor de la patentabilidad del invento de que trata el asunto en referencia, me fue notificado por fijación en lista el 10 de septiembre de 2013. Por lo tanto, la presente defensa es presentada en tiempo oportuno.

III. RESPUESTA A LAS PETICIONES

Me opongo a las peticiones de la sociedad opositora y en consecuencia, solicito a ese Despacho que con fundamento en las consideraciones de hecho y de derecho que se

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presentan en este escrito se declare sin fundamento la oposición presentada por la sociedad **LABORATORIO FRANCO COLOMBIANO LAFRANCOL S.A.S.**

En consecuencia, se declare que el invento titulado **USOS TERAPÉUTICOS DE 1-[2,4-DIMETIL-FENILSULFANIL)FENIL]PIPERAZINA** cumple con los requisitos exigidos en el artículo 14, 16 y 18 de la Decisión 486 de la Comisión de la Comunidad Andina y demás normas concordantes.

IV. FUNDAMENTO FÁCTICO DE LA OPOSICIÓN

A continuación procederé a enumerar los argumentos tenidos en cuenta por la sociedad opositora para presentar oposición en contra de la presente solicitud:

4.1. Las composiciones farmacéuticas que se refieren a 1-[2-(2,4-dimetil-fenilsulfanil)fenil]piperazina y sus sales farmacéuticamente aceptables, útiles en el tratamiento de una enfermedad del SNC, son prácticas y eventos totalmente conocidos en la industria farmacéutica. No existe ninguna novedad sobre estos preceptos y mucho menos nivel inventivo.

4.2. La solicitud en curso carece de los requisitos fundamentales para otorgársele el privilegio de patente de invención, particularmente en materia de novedad y/o nivel inventivo si se tienen en cuenta la materia revelada entre otros, documentos como:

ARTIGAS F ET AL: "P.2.c.040 A randomised, double-blind, placebo-controlled, active-referenced study of Lu AA21004 in patients with major depression", EUROPEAN NEUROPSYCHOPHARMACOLOGY, ELSEVIER SCIENCE PUBLISHERS BV, AMSTERDAM, NL, vol. 19, 1 September 2009 (2009-09-01), pages S426-S427, XP026795343, ISSN: 0924-977X
[retrieved on 2009-09-01]
the whole document

WO 2007/144005 A1 (LUNDBECK & CO AS H [DK]; BANG-ANDERSEN BENNY [DK]; FALDT ANDRE [DK]; M)
21 December 2007 (2007-12-21)
claims 15,17

WO 2009/062517 A1 (LUNDBECK & CO AS H
[DK]; TAKEDA PHARMACEUTICALS NORTH A [US];
CHON JIN) 22 May 2009 (2009-05-22)
claims 19,20

V. RESPUESTA A LOS HECHOS Y ALEGATOS

A continuación presento a su Despacho las razones que demuestran que contrario a lo señalado por el apoderado de la sociedad opositora, el invento para el cual se solicita la protección a través de la concesión de la patente en el expediente de la referencia, cumple cabalmente con los requisitos de los artículos 14, 16, 18 y demás normas concordantes de la Decisión 486 de la Comisión de la Comunidad Andina.

Además, los argumentos que aquí se presentan demuestran que los fundamentos de la opositora carecen de fundamento válido y por tanto, no pueden ni deben ser tomados en cuenta para negar la patente solicitada.

5.1. Modificación de la solicitud de acuerdo con el artículo 34 de la Decisión 486:

En primer lugar y con el fin de presentar la materia reivindicada de conformidad con los lineamientos actuales, se ha procedido con la modificación del pliego reivindicatorio. Lo anterior, en virtud del artículo 34 de la Decisión 486, en donde se establece que la modificación de una solicitud puede realizarse en cualquier momento del trámite mientras no implique la ampliación del alcance inicialmente solicitado.

Por lo tanto, se presenta un nuevo pliego reivindicatorio conformado por **7 reivindicaciones**, el cual solicito sea tenido en cuenta al momento de realizar el examen de patentabilidad.

5.2 Con respecto a las observaciones sobre novedad y nivel inventivo realizadas por la parte opositora **LABORATORIO FRANCO COLOMBIANO LAFRANCOL S.A.S.**, manifiesto a ese Despacho que éstas no son adecuadas frente a la metodología que debe adelantarse para determinar la patentabilidad de una solicitud de patente, pues ésta se limita a afirmar que las composiciones farmacéuticas que se refieren a 1-[2-(2,4-dimetil-fenilsulfanil)fenil]piperazina y sus sales farmacéuticamente aceptables, útiles en el tratamiento de una enfermedad del SNC, son prácticas y eventos totalmente conocidos en la industria farmacéutica y aun cuando enumera tres documentos del estado de la técnica, **no indica cual es el relevante para el**

estudio de novedad o nivel inventivo por tratarse del documento más cercano del estado del arte, por lo que no hay un análisis de fondo que permita llegar a conclusiones no sustentadas desde el punto de vista de patentes con respecto a la real ausencia de los requisitos de patentabilidad.

Ahora bien, en cuanto al requisito de novedad, es pertinente destacar lo señalado en el Manual Andino de Patentes página 65:

*“para determinar la novedad de la invención, se debe comprobar **si existen anticipaciones del estado de la técnica que contengan explícitamente todas las características técnicas esenciales de la invención.** El examen de novedad se efectúa comparando elemento por elemento de la invención tal como está definido por las reivindicaciones con los del estado de la técnica.” (Resaltado fuera del texto).*

Asimismo, en cuanto al requisito de nivel inventivo, es pertinente destacar lo señalado por este mismo Manual con respecto a la evaluación del nivel inventivo:

*“La pregunta a contestar es si teniendo en cuenta el estado de la técnica en su conjunto existe alguna **indicación que lleve a la persona versada en la materia a modificar o adaptar el estado de la técnica más cercano para resolver el problema técnico,** de tal forma que llegue a un resultado que estuviera incluido en el tenor de la(s) reivindicación(es)”. (Resaltado fuera del texto).*

De esta manera, es claro que para la evaluación de novedad y nivel inventivo respectivamente, se deben señalar los documentos más cercanos del estado del arte **en los cuales se revela explícitamente todas las características técnicas de la invención y/o revelan sugerencias y enseñanzas claras para el técnico en la materia que lo lleven a obtener la presente invención.**

5.3 Al respecto, reitero que aun cuando en el escrito de oposición presentado por **LABORATORIO FRANCO COLOMBIANO LAFRANCOL S.A.S.** se citan varios documentos del estado del arte, no se sigue el procedimiento para determinar si una invención cumple con los requisitos legales exigidos. Para ser pertinentes en la evaluación de la novedad y el nivel inventivo de la presente invención, la parte opositora debió señalar las partes de los documentos más cercanos del estado del arte, donde se revelen las características técnicas

de la invención que se tramita en el presente expediente y/o sugerencias y enseñanzas claras para el técnico en la materia que lo llevarían a obtener las mismas.

El opositor no debe basarse en apreciaciones personales sino que toda objeción respecto a la falta de novedad y nivel inventivo debe probarse a partir del estado de la técnica. En particular, el opositor tienen la carga de demostrar a partir de lo revelado en el estado del arte que la invención en su integridad ya se encontraba allí revelada o que una persona versada en la materia habría propuesto las características técnicas que distinguen la invención reivindicada y que permiten alcanzar los resultados obtenidos por la misma.

Sin embargo, insisto en que la sociedad opositora **LABORATORIO FRANCO COLOMBIANO LAFRANCOL S.A.S.** se limita a afirmar que la solicitud de patente de la referencia no cumple con los requisitos de patentabilidad, pero no efectúa un estudio juicioso con base en el estado del arte más cercano.

Así entonces, resultaría claro que la presente solicitud de patente no solo es novedosa sino también inventiva frente a los argumentos citados por la parte opositora **LABORATORIO FRANCO COLOMBIANO LAFRANCOL S.A.S.**, por cuanto no se menciona algún documento que divulgue el método de preparación y la composición farmacéutica oral aquí reivindicados.

En consecuencia, resultaría procedente que se revisara los requisitos mínimos desde el punto de vista técnico que una oposición debe cumplir a efecto de que la misma sea admitida por el Despacho pues simples afirmaciones no relevantes y carentes de sustento alguno, en los términos aceptados en materia de patentes, no surten la finalidad atribuida a este tipo de procedimientos.

5.4. Adicionalmente, llamo la atención de ese Despacho sobre el hecho de que con las modificaciones realizadas al capítulo reivindicatorio, se acentúa la novedad y el nivel inventivo de la invención reivindicada por mi representada, si se tiene en cuenta lo siguiente:

5.4.1 El problema técnico resuelto por la invención que se tramita en la presente solicitud corresponde a la un tratamiento para enfermedades del SNC (por ejemplo, depresión) que está asociado con poco o ningún aumento de peso, tal y como consta en la página 5 de la descripción. Una solución para este problema sería una ventaja para los pacientes que no pueden o no podrán tolerar aumento de peso como parte de su tratamiento, bien sea porque el aumento de peso pondrá en peligro su calidad de vida o ya sea porque el paciente,

adicionalmente a la enfermedad del SNC, también sufre de por ejemplo, diabetes tipo II o hipertensión.

Los ejemplos 1 y 2, páginas 20 y 22 de la descripción, muestran datos de dos estudios controlados con placebo a largo plazo en donde se investigó el efecto de 1-[2-(2,4-dimetil-fenilsulfanil)fenil]piperazina en la prevención de recaídas en los pacientes que sufren de trastorno depresivo mayor o trastorno de ansiedad generalizada, respectivamente.

Los pacientes se trataron por hasta 64 y 56 semanas, respectivamente. En particular, el efecto del compuesto de piperazina en el peso se observó y comparó con el del placebo. La conclusión de los dos ensayos es clara, por ejemplo, no hay una diferencia significativa entre el placebo y el compuesto de piperazina en lo que se refiere al aumento de peso. A partir de esto se puede concluir que los datos presentados en la solicitud hacen que, por lo menos, sea probable que el problema técnico de la invención haya sido resuelto.

Así, por ejemplo el documento WO 2007/144005 mencionado por la opositora revela que el compuesto de piperazina de la invención en un ensayo clínico de 8 semanas no resultó en cambios clínicamente relevantes por ejemplo, en peso. **Sin embargo, esta divulgación no llevaría a la persona versada en la materia a sugerir que el compuesto de piperazina de la invención pueda usarse en el tratamiento de largo plazo con poco o sin aumento de peso, o en el tratamiento de pacientes “sensibles al peso”.**

En el texto de la descripción se señala que no es posible concluir algo en relación a los efectos de los antidepresivos sobre el peso a largo plazo con base en las observaciones hechas en estudios de corto plazo. Los estudios de corto plazo con paroxetina han demostrado ausencia de aumento de peso o incluso la pérdida de peso. Esto debe contrastarse con las experiencias a largo plazo con paroxetina que muestran un aumento marcado de peso (página 3, línea 17 a 27 de la descripción). Del mismo modo, la experiencia a partir de estudios de corto plazo con fluoxetina es que este compuesto da lugar a una pérdida de peso. Esto debe compararse con las experiencias a partir de estudios de largo plazo en los que la fluoxetina no da lugar a un aumento de peso (página 4, línea 9 a 12 de la descripción) o a un marcado aumento en el peso (página 3, línea 3 a 11 de la descripción). La conclusión que debe elaborarse a partir de estas observaciones es que los datos sobre el aumento de peso en estudios de corto plazo no pueden usarse para predecir el aumento de peso en tratamientos de largo plazo. La solicitud en la descripción, página 4, línea 17 a página 5, línea 8, ofrece sugerencias de por qué esto es así. Un mayor apoyo a esta conclusión también puede encontrarse en *“Dialogues in Clinical Neuroscience”*, 10, página 409 a 418, del cual se anexa una copia. En la página 11, columna de la derecha se discute el periodo de

tiempo para ciertos efectos secundarios al comenzar, concluyendo que *"Por otra parte, algunos efectos secundarios como náuseas, empiezan temprano en el curso del tratamiento y luego usualmente mejoran, mientras que otros como el aumento de peso no se presentan inicialmente sino que surgen con el tiempo".* (Subrayado fuera del texto).

Para esta discusión también es útil tener en cuenta que el periodo de tratamiento para muchas enfermedades del SNC, como la depresión, es significativamente más largo que un periodo de 8 semanas como el estudiado en WO 2007/144005. Adjunto adicionalmente un fragmento de *"Maudsley Prescribing Guidelines"*, 9 Edición, 2007, en el cual se indica en la página 186, que los pacientes con depresión deben tratarse por al menos 4-6 meses después de la resolución de los síntomas. Si el paciente ha sufrido previamente de depresión, debe tratarse por al menos 2 años. Del mismo modo, las recomendaciones sobre cómo tratar ansiedad en la página 251 también se recomienda un tratamiento con duración de al menos 6 meses.

Adicionalmente, presento con este escrito el documento *"Vortioxetine: A new antidepressant choice in the United States"*, Medscape, Octubre 2, 2013, en el que se reconoce el perfil de ganancia de peso benigno de vortioxetine (Brintellix®), producto aprobado por la FDA. En el último párrafo de este documento se indica: "Por otra parte, su perfil de seguridad indica que vortioxetine puede ser particularmente beneficioso para los pacientes que experimentaron un aumento de peso, sedación y/o efectos secundarios sexuales, en relación con otros antidepresivos". Por lo tanto se demuestra que la solución al problema técnico planteado en la presente solicitud fue logrado, esto es, un tratamiento para enfermedades del SNC (por ejemplo, depresión) que está asociado con poco o ningún aumento de peso.

5.4.2 Por todo lo anterior, una persona versada en la materia no hubiera podido predecir nada acerca de los efectos del compuesto de piperazina sobre el peso a largo plazo con base en la divulgación de los efectos de corto plazo de WO 2007/14405. Adicionalmente, la persona versada en la materia sería consciente del hecho de que el aumento de peso es un evento adverso observado generalmente, asociado con el tratamiento con antidepresivos. Para llegar a las reivindicaciones de la presente solicitud, por lo tanto se requiere de actividad inventiva. Adicionalmente, los datos presentados en la solicitud muestran claramente que el problema técnico de la presente invención se ha resuelto de manera favorable. Por lo tanto, se afirma que las reivindicaciones actualmente en archivo son inventivas.

5.5. Por lo tanto, las reivindicaciones de la presente solicitud, resultan novedosas e inventivas en vista de los documentos del estado del arte citados por la sociedad opositora,

debido a que ninguno de estos documentos da a conocer o sugiere que el compuesto de piperazina de la invención pueda usarse en el tratamiento de largo plazo con poco o sin aumento de peso, o en el tratamiento de pacientes “sensibles al peso.

5.6. En consecuencia, ese Despacho puede apreciar que los documentos citados como anterioridades por la sociedad opositora, no describen la invención acá reivindicada y tampoco hay sugerencias que permitan a una persona medianamente versada en la materia, referirse a ellos para resolver el problema técnico planteado por la solicitud de mi representada. Por lo tanto la materia objeto de protección como patente de invención que se tramita en el presente expediente goza de los requisitos de novedad y nivel inventivo.

VI. PETICIONES

Con fundamento en lo anterior solicito a ese Despacho lo siguiente:

6.1 Declarar infundada la oposición presentada por la sociedad **LABORATORIO FRANCO COLOMBIANO LAFRANCOL S.A.S.**

6.2 Declarar que el invento titulado **“USOS TERAPÉUTICOS DE 1-[2,4-DIMETIL-FENILSULFANIL)FENIL]PIPERAZINA”** para el cual mi representada solicita el otorgamiento de la patente de invención cumple con los requisitos del artículo 14 y concordantes de la Decisión 486 de la Comisión de la Comunidad Andina.

6.3 Otorgar el privilegio de patente de invención para **“USOS TERAPÉUTICOS DE 1-[2,4-DIMETIL-FENILSULFANIL)FENIL]PIPERAZINA”** a favor de **H. LUNDBECK A/S.**

VII. ANEXOS

Anexo a este escrito los siguientes documentos:

- 7.1. Formulario de Modificaciones y/o Correcciones;
- 7.2. Recibo por concepto de modificaciones de solicitud en trámite.
- 7.3. Nuevo capítulo reivindicatorio conformado por 7 reivindicaciones.

- 7.4. Dialogues in Clinical Neuroscience”, 10, página 409 a 418: “Toward achieving optimal response: understanding and managing antidepressant side effects”, Karen Kelly, MD; Michael Posternak, MD; Jonathan E. Alpert, MD, PhD.
- 7.5. The Maudsley, Prescribing Guidelines”, 9 Edición, 2007.
- 7.6. Medscape, “Vortioxetine: A new antidepressant choice in the United States, Christoph U. Correll, MD, 2 de octubre de 2013.

VIII. NOTIFICACIONES

Mi representada y yo recibiremos notificaciones en la Secretaría de su Despacho o en mi oficina de abogada ubicada en la Carrera 4ª No. 72-35 de la ciudad de Bogotá, D.C.

Señor Director,


LUZ CLEMENCIA DE PAÉZ

C.C. No. 35.456.344 de Usaquén

T.P.A. No. 23.555

COLO-03003-0841-125-9
COLO-03003-0264-027-5
JGG\JGG\ID-256289\WPCL3003
No. M-2013-256289\JGG

 Industria y Comercio SUPERINTENDENCIA	Espacio reservado para el adhesivo de radicación
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DIRECCIÓN DE NUEVAS CREACIONES
MODIFICACIONES Y/O CORRECCIONES

1. Identificación del Trámite

☐ Error material

☒ Modificación a una Solicitud en trámite

☒ Patente de Invención

☐ Patente de Modelo de Utilidad

☐ Registro de Diseño Industrial

☐ Esquema de Trazado de Circuitos Integrados

2. Datos del solicitante

Persona Natural

☐

Persona Jurídica

☒

H. LUNDBECK A/S

Nombre o denominación / Nombre o razón social completa

Nombre representante legal

Tipo de empresa Micro ☐ Pequeña ☐ Mediana ☐ Otra ☐

Documento de identificación: ☐ C.C. ☐ C.E. ☐ NIT ☐ Otro Número _____

Nacionalidad/País de constitución	Dirección y domicilio del titular	Ciudad
Dinamarca	9 Ottliavej, Valby DK-2500, Dinamarca	Valby
Dirección electrónica	No. Fax	Número telefónico
clientes@cavelier.com	2 11 86 50	3 47 36 11

☐ Autorizo expresamente a la Superintendencia de Industria y Comercio para que todas las comunicaciones sean enviadas a través de la dirección de correo electrónico

3. Datos del apoderado:

Apellidos y Nombre

Documento de identificación

Tarjeta profesional

De Páez Luz Clemencia

C.C. 35.456.344

T.P.A. 23.555

Dirección y domicilio	Ciudad	
Carrera 4ª No. 72 –35	Bogotá	
Dirección electrónica	No. Fax	Número telefónico
cavelier@cavelier.com	2 11 86 50	3 47 36 11

En caso de haber presentado poder general para asuntos que se adelanten ante la Delegatura de Propiedad Industrial, sírvase indicar el número de su radicación o protocolo de poder general

4. Datos del trámite

Corrección:

Expediente No 13.035.030

Aparece

Debe ser

Modificación:

- ☒ **Modificación al capítulo reivindicatorio.**
Presento nuevo capítulo reivindicatorio compuesto por 7 reivindicaciones y pido respetuosamente que el examen de patentabilidad sea realizado sobre estas nuevas reivindicaciones presentadas. Respetuosamente manifiesto que a pesar de eliminar materia del pliego reivindicatorio originalmente presentado, mi representada no renuncia a la protección que pueda obtener sobre dicha materia y además se reserva el derecho de presentar una solicitud divisional que la contenga durante el trámite de la presente solicitud, beneficiándose de la fecha de prioridad inicialmente reivindicada.
- ☐ **Modificación al capítulo descriptivo.**
- ☐ **Modificación al resumen.**
- ☐ **Modificación a los dibujos.**

5. Anexos

- ☒ Comprobante de pago de la tasa para la presentación de la corrección y/o modificación.
- ☐ Poder, si fuere el caso.
- ☒ Documento que contiene las modificaciones o correcciones.
- ☐ Copia de la solicitud y sus anexos en formato magnético.

6. Firma

Nombre y apellidos

LUZ CLEMENCIA DE PAEZ

C.C. 35.456.344 DE Usaquén

Firma

Luz Clemencia de Paez

Tarjeta Profesional 23.555

REIVINDICACIONES

1. 1-[2-(2,4-dimetil-fenilsulfanil)fenil]piperazina y sus sales farmacéuticamente aceptables para uso en el tratamiento a largo plazo de una enfermedad del SNC en un paciente, donde dicho tratamiento está asociado con un ligero aumento de peso o con ningún aumento de peso.

2. 1-[2-(2,4-dimetil-fenilsulfanil)fenil]piperazina y sus sales farmacéuticamente aceptables para uso en el tratamiento de una enfermedad del SNC en un paciente quien ha recibido previamente medicación para el tratamiento de dicha enfermedad, cuya medicación fue interrumpida debido a eventos adversos relacionados con el peso.

3. 1-[2-(2,4-dimetil-fenilsulfanil)fenil]piperazina y sus sales farmacéuticamente aceptables para utilizar en el tratamiento de una enfermedad del SNC en un paciente que tiene sobrepeso.

4. 1-[2-(2,4-dimetil-fenilsulfanil)fenil]piperazina y sus sales farmacéuticamente aceptables de acuerdo con la reivindicación 3, donde dicho paciente se caracteriza por un IMC superior a 25.

5. 1-[2-(2,4-dimetil-fenilsulfanil)fenil]piperazina y sus sales farmacéuticamente aceptables para uso en el tratamiento de una enfermedad del SNC en un paciente que también sufre de diabetes tipo II, hipertensión o cardiopatías coronarias o se está absteniendo de consumir nicotina.

6. 1-[2-(2,4-dimetil-fenilsulfanil)fenil]piperazina y sus sales farmacéuticamente aceptables de acuerdo con cualquiera de las reivindicaciones 1-5, donde dicha enfermedad del SNC se selecciona entre depresión, ansiedad, dolor crónico y toxicomanía.

7. 1-[2-(2,4-dimetil-fenilsulfanil)fenil]piperazina y sus sales farmacéuticamente aceptables de acuerdo con cualquiera de las reivindicaciones 1-6 que es la sal bromhidrato.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800.176.089-2

-/-

Industria y Comercio
SUPERINTENDENCIA

RECIBO DE CAJA

No. 13 - 124134

Bogotá D.C., Diciembre 03 de 2013 - 11:19:29

RECIBIDO DE : CAVELIER ABOGADOS

NI 860.041.367

*** Soporte del Pago ***

TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR. PAGO
CONSIGNACION	BANCO DE BOGOTA	062754387	650544845	03/12/2013	9.786.000.00

*** Conceptos Pagados ***

CANT.	RENTISTICO	CONCEPTO	Vr.UNDITARIO	Vr.CONCEPTO
1	50005-01-03	CAMBIO DE MODALIDAD Y MODIFICACIONES SOLICITUD MODIFICACIONES CAMBIO SOLICITANTE POR CESION	125.000.00	125.000.00
				\$125.000.00

SON: **CIENTO VEINTICINCO MIL PESOS MONEDA CORRIENTE***

Responsable: _____

Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 13-035030- -00007-0000

Fecha: 2013-12-04 16:27:52 Dep. 2020 DIR.NUEVASCR
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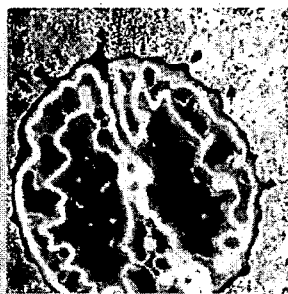
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Toward achieving optimal response: understanding and managing antidepressant side effects

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The safety and tolerability of antidepressants have improved considerably over the past two decades. Nevertheless, antidepressant side effects are still common and problematic. The majority of patients treated with contemporary agents experience one or more bothersome side effects. These side effects often create barriers to achieving depressive remission, as well as to preventing relapse and recurrence. Clinicians tend to underestimate the prevalence of side effects, and as many as one quarter of patients discontinue their antidepressants because of difficult-to-tolerate side effects; others may continue on antidepressant therapy but experience diminished quality of life related to troublesome side effects. This article reviews the prevalence of side effects, the impact of side effects on treatment adherence, and methodological issues including the challenge of distinguishing side effects from residual depressive symptoms, discontinuation effects, and general medical problems. In addition, we address the most common side effects such as sexual dysfunction, gastrointestinal problems, sleep disturbance, apathy, and fatigue, and offer strategies for management that may help patients achieve optimal response to pharmacotherapy.

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Despite advances over the past two decades in the tolerability and safety of antidepressant treatment with the development of the selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), and other agents, antidepressant side effects continue to pose considerable challenges to treatment. Side effects sometimes exacerbate or masquerade as residual depressive symptoms, and often precipitate premature discontinuation or the use of subtherapeutic doses of antidepressants. In the following review we describe the scope of antidepressant side effects and their impact on treatment adherence, methodological issues concerning the study of side effects, and the most common side effects and approaches to management. Anticipating, recognizing, and vigorously managing antidepressant side effects are crucial avenues for achieving remission in depression as well as preventing relapse and recurrence.

Prevalence and impact of side effects

Despite considerable improvements in side-effect profiles, antidepressants continue to be associated with a significant burden of side effects that affect treatment adherence and quality of life. Hu et al¹ studied 401 patients with depression who had recently been prescribed an SSRI, and found that after 75 to 105 days of

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treatment, 86% of patients reported at least one side effect, and 55% experienced one or more bothersome side effects. Interestingly, physicians appear to underestimate the rate of side effects with antidepressants. In a survey of physicians and the patients to whom they had prescribed SSRIs,² physicians underestimated the overall rate of side effects as well as the frequency of specific side effects such as dry mouth, dizziness, drowsiness, headache, insomnia, rash or itching, blurred vision, diarrhea, and weight loss when compared with the actual rate reported by their patients. That clinicians underestimate the prevalence of side effects likely contributes to inadequate communication before and during prescription of antidepressants.

The impact of side effects on achieving depressive remission and on therapy adherence is great. In a study by Demyttenaere et al³ of 272 outpatients receiving antidepressant therapy, 53% had discontinued treatment by the end of the 6-month study. Of these patients, 23% cited "adverse events" as the reason for their discontinuation. In a similar study, Hu et al¹ found that 33% of patients had discontinued their treatment by the end of a 105-day period, with the most often-cited reason being adverse effects (36%). This study found that the presence of multiple side effects or the presence of side effects deemed extremely bothersome by patients significantly increased the odds of discontinuation. In addition to disrupting the goal of achieving a minimally adequate course of antidepressant treatment for achieving remission and preventing relapse and recurrence, side effects frequently impede adequate dose titration, necessary for delivering a full therapeutic dose. Although precise estimates are difficult to find, it is a frequent clinical observation that patients struggling with side effects often remain on lower-than-optimal doses for long periods of time, during which their depression is inadequately treated. In addition, bothersome side effects such as somnolence or sexual dysfunction, even when they do not lead to premature drug discontinuation or inadequate dosing, clearly compromise quality of life.

Methodological issues

There are considerable methodological challenges related to the study and clinical management of side effects. When evaluating side-effect data, it is important to consider whether the information was obtained by spontaneous report, self-report checklists, or responses

to direct questioning. Spontaneous reporting of side effects following an open-ended question (eg, "any change since last visit?") typically yields a lower incidence of adverse events than itemized self-report checklists (eg, the Frequency, Intensity, and Burden of Side Effects Rating (FIBSER) Scale⁴) or direct questioning about specific side effects (The Systematic Assessment for Treatment Emergent Events-Specific Inquiry [SAFE-SI]⁵). The reporting of certain side effects, particularly sexual dysfunction, may also be influenced by the degree of comfort the patient/subject has with the subject area and with the questioner; this may be affected by gender, culture, and other factors. Side-effect rates presented for an antidepressant in isolation tend to be of somewhat limited benefit, as common experiences such as headache or rhinitis inevitably figure prominently, even if they bear no specific relationship to the agent. Hence, side effects presented as placebo-adjusted rates are often more informative. So too are comparative rates of specific side effects across a number of antidepressant agents, which allow clinicians and patients to make informed choices about the relative risks of side effects of greatest concern to the patient.

In both research and clinical contexts, an important challenge is presented by the phenomenological overlap between side effects and residual symptoms of depression. Thus, fatigue, cognitive impairment, apathy, jitteriness and irritability, and sleep and appetite changes are core features of depression, but may also be related to antidepressant treatment. In a small study of 43 depressed inpatients,⁶ which investigated the rate of somatic symptoms and complaints that were present before and after treatment, many symptoms often considered to be side effects of drugs were also present prior to treatment, including dry mouth, lightheadedness, sweating, tremors, and constipation. The distinction between residual symptoms and side effects is crucial, as they call for very different responses. In the latter case, a dose increase or pharmacological or other augmentation of treatment may be required. In the former case, a dose reduction or use of a pharmacological antidote would be important initial considerations. A careful delineation of depressive symptoms prior to the initiation of antidepressant treatment, such as with the use of a structured rating scale such as the Inventory for Depressive Symptomatology,⁷ is particularly helpful as a supplement to clinical judgment to determine which adverse events are truly treatment-emergent and which may reflect per-

sisting, inadequately responsive symptoms of depression. Conversely, in some instances, an experience recorded as an adverse event may have been related to depressive improvement; this is particularly true in an individual whose increased weight following a period of anorexia related to depression might be more accurately construed as normalization than weight gain.

An additional, frequently overlooked factor that may confound interpretation of apparent adverse events has to do with discontinuation-emergent effects of antidepressants, which can resemble antidepressant side effects and/or residual symptoms. Thus, for example, a patient with intermittent noncompliance on antidepressants such as venlafaxine or paroxetine that are associated with common discontinuation-related syndromes may experience malaise or nausea after a day or two off medication without being aware of their relationship to abrupt drug discontinuation. Fortunately, when patient history raises the possibility that apparent side effects or residual symptoms are attributable to inconsistent dosing, the hypothesis can be simply tested if the patient is willing to commit to more regular dosing. In the case of forgetful patients, daily pillboxes or newer technologies such as electronic caps that remind the patient of skipped doses are often helpful. In other patients, education about discontinuation effects and/or efforts to address possible ambivalence about use of medications may reduce instances of medication cessation.

Side effects most likely to cause drug discontinuation

An understanding of which side effects occur most frequently and which of these are most likely to lead to patient nonadherence enhances one's ability to choose a drug and counsel patients. The most common side effects reported by patients in the study by Hu et al¹ of 401 outpatients taking SSRIs were drowsiness (38%), dry mouth (34%), and sexual dysfunction (34%). This study, which was conducted in 1999-2000, questioned patients about side effects via phone interviews within 75 to 105 days of starting antidepressant therapy. The side effects deemed most bothersome were sexual dysfunction (17%), drowsiness (17%), and weight gain (11%). While these were the most common, Lin et al⁸ looked at which side effects were most likely to lead to discontinuation in their naturalistic study of 155 outpatients on antidepressant therapy (a tricyclic antidepressant, tra-

zodone, or fluoxetine). They found that severe daytime sleepiness showed a significant association with early discontinuation, and if experienced to a degree deemed severe by patients, fatigue, blurred vision, insomnia, anxiety, appetite changes, and weight gain were all significantly associated with discontinuation in months two and three of treatment.

Time period of side effects

To further understand side effects and their impact on patients' quality of life and compliance, it is also important to be aware of the time when certain side effects present. While there is common belief that side effects can be classified as acute or chronic, a review by Papakostas⁹ challenged this idea. In it, he cites Hu et al's¹ study that shows that although certain side effects may present early or later in the course of treatment, many of those that are considered acute persist to a point that they should be considered chronic. In this study, SSRI-induced side effects such as insomnia, sexual dysfunction, and drowsiness that are often considered acute persisted at 3 months. On the other hand, some side effects such as nausea do start early in the course of treatment and then usually improve, while others such as weight gain are not present initially but emerge over time. Another naturalistic study by Demyttenaere et al³ of 272 outpatients on an SSRI, trazodone, venlafaxine, or moclobemide looked at the time period that patients discontinue treatment secondary to side effects, and found that patients who cited side effects as their reason for discontinuation dropped out of treatment at a mean period of 6.5 weeks. This study showed that side effects and lack of efficacy led to the earliest discontinuation of antidepressants (at 6.5 weeks and 7 weeks respectively), followed by other reasons such as "fear of drug dependence" and "feeling better" that occurred at 8 weeks and later. Reinforcing the conclusion that side effects often account for early discontinuation, Bull et al¹⁰ found that significantly more patients discontinued or switched their SSRI because of an adverse effect within the first 3 months of treatment compared with the second 3 months.

Side effects as predictors of response

Although there are no systematic studies to our knowledge that address specific treatment-emergent adverse effects as predictors of response, we are aware that opti-

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mistic colleagues sometimes look for certain early side effects, such as activation or insomnia, as favorable prognosticators. Emerging biomarkers, such as quantitative electroencephalography¹¹ or neuroimaging,¹² alone or in conjunction with clinical features at baseline and during treatment, represent an important area of current research. Nevertheless, while the presence of particular side effects has no known prognostic significance, when patients have no side effects and minimal response despite full doses of an antidepressant, it is reasonable to re-evaluate medication adherence as well as to consider the possibility of drug-drug interactions (particularly metabolic induction) and genetic polymorphism that might call for higher doses to achieve an optimal outcome.

Common side effects and their management

Given the impact of side effects on treatment adherence, response, and quality of life, an understanding of the management of common side effects is imperative for optimal management of depressed outpatients. Successful management of side effects enhances adherence, permits adequate dosing, improves patient comfort and function, and prevents premature discontinuation of therapy. Appropriate management includes thoughtful drug selection, the anticipation of common and rare but serious side effects with patients, and striving for the lowest effective dose and simplest drug regimens consistent with appropriately vigorous treatment. It also includes the addition of appropriate adjunctive therapies to manage emergent complaints.

Fatigue and somnolence

Fatigue or drowsiness is a common side effect experienced by 10% to 38% of antidepressant-treated outpatients.^{1,13} In one study of 401 outpatients,¹ 70% of people who experienced fatigue had it by 2 weeks, and 63% continued to experience it at 3 months. In comparative studies, SSRIs had a higher rate of sleepiness than bupropion¹⁴ and the noradrenergic reuptake inhibitor, reboxetine,¹⁵ and equivalent rates as nefazodone,¹⁶⁻¹⁸ venlafaxine,¹⁹⁻²¹ and duloxetine²²⁻²³ and the reversible monoamine oxidase inhibitor moclobemide.²⁴ Mirtazapine²⁵ and trazodone²⁶ are associated with greater rates of somnolence and fatigue than SSRIs. The differential of drowsiness should include residual symptoms of

depression, a primary sleep disorder such as obstructive sleep apnea or restless leg syndrome or altered sleep cycle, and substance-use disorders. Management of drowsiness includes careful evaluation of sleep patterns and counseling on sleep hygiene measures (such as avoidance of daytime napping), changes in antidepressant dosing schedule such as a shift from morning to nighttime administration, divided dosing or use of a slower release preparation, as well as pharmacological management with psychostimulants, modafinil, bupropion, reboxetine, or protriptyline, or consideration of alternative remedies such as methylfolate or S-adenosylmethionine. For some patients, a graduated increase in exercise may also help reduce fatigue.

Sexual dysfunction

Sexual dysfunction is a common long-term problem on antidepressants. Medication side effects typically affect libido, arousal, orgasm, and ejaculation,²⁷ and may affect lubrication and erection. These side effects have traditionally been greatly underreported, largely related to patients' and clinicians' reticence to address this topic. In a study of 344 patients by Montejo-Gonzalez et al,²⁸ 58% of patients reported sexual dysfunction when physicians directly inquired, compared with only 14% of those who spontaneously reported sexual dysfunction. In a naturalistic study that directly inquired about side effects through closed-ended questions,¹ 34% of patients reported sexual dysfunction, with half of these patients (17% of the overall group) deeming it bothersome. Seventy percent of patients who experienced sexual dysfunction did so by 2 weeks, with 80% experiencing it at 3 months.

There are clear differences among antidepressant agents in rates of sexual dysfunction. Bupropion immediate-release and nefazodone were found to have the lowest rate of sexual dysfunction in a study of more than 6000 individuals on SSRIs, bupropion, mirtazapine, nefazodone, reboxetine, and venlafaxine.²⁹ Studies comparing SSRIs with mirtazapine are inconclusive, some showing higher rates of sexual dysfunction with SSRIs and others with mirtazapine.³⁰⁻³⁵ Among the SSRIs, paroxetine has been found to have the highest rates of sexual dysfunction.³⁵

Management of sexual dysfunction, like all side effects, begins with a thorough assessment during the initial evaluation to establish a baseline, including discussion

of whether the patient is sexually active and the degree of satisfaction with sexual function prior to treatment, and to discuss concerns about possible sexual dysfunction related to anticipated treatment. It is important to reassess sexual function periodically during the course of therapy, and also to recognize that sexual function may become increasingly important to patients as their depressive symptoms improve.³⁶ Prior to the introduction of sildenafil and similar agents, many methods and medications were used in an attempt to treat the sexual side effects of antidepressants. These included dose reduction, timing of sexual activity toward the end of a dosing interval, several days' drug holiday,³⁷ and antidote therapy with medicine such as psychostimulants³⁸ and dopamine (DA) agonists such as amantadine, pramipexole and Dexedrine, norepinephrine (NE)/DA agents such as bupropion, serotonin (5-HT)₂ receptor antagonists such as nefazodone, and α_2 -adrenergic receptor antagonists such as yohimbine.³⁹⁻⁴⁰ As sildenafil has proven effective in placebo-controlled trials in the treatment of sexual performance,⁴¹ this agent and related phosphodiesterase V inhibitors have become the mainstay of management of sexual function. A recent trial⁴² also demonstrated that sildenafil is effective at decreasing adverse sexual effects in women taking SSRIs, including improvement in desire, arousal-sensation, arousal-lubrication, orgasm, and enjoyment. Nevertheless, many patients do not respond sufficiently well to sildenafil and related agents or other attempted antidotes, and efforts to identify other remedies continue. These include complementary and alternative treatments such as maca root, arginine-containing compounds, and ginkgo biloba. When sexual dysfunction persists despite efforts at dose adjustments and antidote therapy, the principal option is to consider switching to agents with lesser degrees of sexual dysfunction, typically bupropion, or, where available, reboxetine. Nefazodone is another option, though its use has been limited by risk of rare but serious hepatotoxicity.

Gastrointestinal problems

Nausea and stomach upset

Nausea and stomach upset are also common side effects of antidepressant treatment, present in 17% to 26% of patients taking it,^{1,13} 83% of whom experienced it by 2 weeks, and 32 % of whom continued to experience it at

3 months. Treatment with SSRIs was associated with a higher rate of nausea than bupropion,⁴³ moclobemide,²⁴ mirtazapine,²⁵ and reboxetine.¹⁵ Equivalent rates were found between SSRIs and trazodone,^{26,44} nefazodone,¹⁶⁻¹⁸ and duloxetine.²²⁻²³ Venlafaxine has been found to have a higher incidence of nausea than SSRIs.⁹ Some studies have found that nausea from venlafaxine and paroxetine may be reduced using controlled-release formulations.⁴⁵ The management of nausea and vomiting includes the use of divided dosing or taking medications with a small amount of food, such as crackers or toast. Some patients benefit from ginger-containing foods and beverages, histamine 2 antagonists such as ranitidine,⁴⁶ or proton pump inhibitors such as omeprazole. Adjunctive promethazine, prochlorperazine, or ondansetron also have been shown to be beneficial, as has mirtazapine because of its 5-HT₃ receptor antagonistic properties.

Diarrhea

Diarrhea may also occur as a side effect of antidepressant treatment. As with the other gastrointestinal side effects of antidepressants, it may be a transient effect and resolve within weeks, but it also may persist in some patients. A meta-analysis of 84 trials¹³ found that overall, 16% of patients taking SSRIs experienced diarrhea. Hu et al¹ found a rate of 15% of patients who experienced diarrhea, 78% of whom experienced it at 2 weeks and 45% of whom still experienced it at 3 months. Management of diarrhea can include antidiarrheal agents such as loperamide, or diphenoxylate hydrochloride. Cyproheptadine, Lactobacillus acidophilus culture, and psyllium may also be helpful.

Constipation

Constipation may emerge during antidepressant therapy. Of the SSRIs, paroxetine has been associated with the highest rates of constipation, presumably secondary to its high affinity for muscarinic receptors.⁴⁷ Overall, the rate of constipation has been found to be 11% to 12.5%,^{1,13} with 4.7% of patients describing it as a bothersome side effect.¹ Constipation can often be controlled with adequate activity, fluid, and fiber intake. When pharmacological management is required, bulk-forming laxatives, stool softeners, osmotic agents, bethanechol, and cholinesterase inhibitors may be used.⁴⁶

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Weight gain

Another bothersome effect of antidepressant treatment that may interfere with treatment adherence and general health is weight gain. This is also an effect that is often difficult to study because it can be a sign of improvement in patients who have weight loss as a symptom of depression, a residual symptom in patients who overeat when depressed, or something independent of depression or its treatment. For this reason, it is important to look at placebo rates of weight gain when evaluating these rates in patients. There are various ways that weight gain is studied and reported, including as the percentage of weight gain from baseline or as rate of weight gain greater than 7% from baseline. Although complaints of weight gain often emerge late in treatment, there are relatively few studies that have systematically assessed this side effect on long-term treatment and fewer that have had the opportunity to compare weight gain on active treatment with that on placebo.⁴⁸ Many of the long-term studies show no difference between SSRIs and placebo, except for paroxetine, showing a significant difference from placebo.^{49,50} There was no drug/placebo difference in weight gain in a study looking at fluoxetine over 26 weeks of continuation treatment⁵¹ or in a 6-month duration study of citalopram.⁵² In a study comparing the rate of weight gain on antidepressants,⁹ mirtazapine was associated with the highest percentage of patients with weight gain (26%), followed by SSRIs and venlafaxine (16% to 19%). Nefazodone,⁵³ bupropion,⁵⁴ and reboxetine⁵⁵ result in the lowest rates of weight gain during treatment. Among tricyclic antidepressants, the secondary amine tricyclics, such as desipramine, nortriptyline, and protriptyline, have generally been associated with lower weight gain than the tertiary amine agents such as imipramine, amitriptyline, and clomipramine.

The management of antidepressant-associated weight gain is challenging and should begin with the choice of drug. Clinicians should try to identify patients who are at risk for weight gain based on medical history and lifestyle, and these patients should be targeted for dietary and physical activity interventions. The addition of bupropion, topiramate, zonisamide, or sibutramine may also be considered. As weight gain may not be dose-dependent, at least within the therapeutic range of doses, a modest dose reduction is often ineffective. In the setting of unacceptable weight gain that is not responsive to dietary and behavioral modifica-

tions, a switch to an agent with a lower propensity for weight gain is a primary consideration.

Insomnia

Rates of insomnia have been found to be 12% to 22% (antidepressants administered to outpatients with MDD, enrolled in clinical trials who report insomnia as a treatment emergent side effect),^{1,13} with 11% of patients deeming it bothersome. Sixty-four percent of patients who experienced insomnia experienced it by 2 weeks, and 56% continued to experience it at 3 months.¹ In a review of antidepressant-induced side effects, Papakostas⁹ cites higher rates of insomnia with SSRIs than with mirtazapine, trazodone, and nefazodone, and equivalent rates between SSRIs and bupropion, moclobemide, duloxetine, and venlafaxine. Reboxetine was found to have a higher rate of insomnia than SSRIs. It is particularly important to rule out primary sleep disorders or concomitant alcohol and other substance abuse when evaluating and managing insomnia. Management of antidepressant-induced insomnia includes educating patients on behavior techniques and sleep hygiene, modification of use of caffeine and common sympathomimetic agents, changing the timing of doses, and adding adjunctive medications including sparing use of benzodiazepines, zolpidem, eszopiclone, melatonin, trazodone, mirtazapine, and/or low doses of anticonvulsants, and atypical antipsychotics.

Tremor

Fine and rapid tremors of the extremities can occur as a side effect of antidepressants. Rates of tremor of SSRIs and venlafaxine are 3 to 5 times higher than placebo, whereas the rate of tremor in nefazodone and mirtazapine therapy is only 2 to 2.5 times higher than placebo.⁵⁶ It is important to consider other agents or causes when assessing a tremor, including caffeine intake and anxiety as well as common antidepressant adjuncts such as the atypical antipsychotics. Decreasing caffeine intake and the use of benzodiazepines and β -blockers can be helpful in the treatment of tremor.

Apathy

The development of apathy or indifference can be a bothersome side effect associated with antidepressant medication. Symptoms that can include amotivation or

dullness often develop slowly, and although the mechanism of this effect is unclear, it may be secondary to an inhibition of dopamine by serotonergic medications.⁵⁷ Apathy is a challenging and elusive complaint to evaluate and may be secondary to drug treatment, a residual symptom, or may herald relapse. Some, but not all, patients are able to point to a distinction between the comfortable detachment they feel when experiencing antidepressant-related apathy in the setting of an otherwise satisfactory response to treatment compared with the more anguished or far-reaching anhedonia and motivational impairment they experience when depressed. If a relapse or residual symptoms are not suspected, management strategies include dose reduction, switching to a different drug or class, typically toward less serotonergic agents, or the addition of a stimulant or dopaminergic drug. Pharmacologic options include methylphenidate or dextroamphetamine, bupropion, amantadine, ropinirole, pramipexole, modafinil, or pergolide.

Discontinuation syndrome

Abrupt discontinuation of SSRIs, nefazodone, venlafaxine, and mirtazapine may precipitate a discontinuation syndrome that can occur hours to days following the termination of medication. The syndrome often includes flu-like symptoms such as malaise, myalgias, nausea, dizziness, and headache, and may even include neurologic symptoms such as unsteady gait, dysesthesias such as unusual shock-like sensations, tremulousness, or vertigo.⁴⁶ Risk factors for discontinuation syndrome include abrupt cessation of short-acting agents and/or agents at a high dose. Indeed, in some patients, some of the features of discontinuation syndrome simply from an abrupt dose reduction rather than actual cessation. As previously noted in this review, discontinuation symptoms may masquerade as side effects of treatment. Discontinuation syndrome may be minimized with the use of a gradual taper schedule. Patient education about the risk of discontinuation symptoms is crucial whenever an antidepressant likely to be associated with discontinuation emergent symptoms is prescribed. Substituting a longer-acting antidepressant, most notably fluoxetine, for a shorter-acting one may also decrease the risk of withdrawal syndrome.⁵⁸ This is particularly helpful for patients who have already demonstrated problems tapering another antidepressant because of discontinuation emergent adverse events. The addition of benzodiazepines for irritability, anxiety, or

sleep disturbance related to discontinuation or nonsteroidal anti-inflammatory agents for pain may improve patient experience. Communication with patients about the short duration of withdrawal symptoms may help patients cope with these typically self-limited symptoms.

Other management techniques for preventing relapse or discontinuation due to side effects

Patient education

A critical component to side-effect management is education of patients prior to prescribing an antidepressant. This should include discussion of common side effects and when they would be most likely to emerge. It is important to discuss with patients which side effects require a prompt evaluation (eg, rash, agitation, worsening suicidality) and which side effects are likely to be self-limiting (eg, mild nausea or jitteriness). Patients may assign a different value to certain side effects than their clinician; given the large number of agents available it is important to reach agreement on how the anticipated risks and benefits of treatment will factor into choice of agent. Patients may harbor certain preconceptions about side effects which can be addressed at this time. Examples of this would include the mistaken belief that side effects necessarily indicate toxicity or indicate that the medication is a poor match for the patient. It is often helpful to let patients know that antidepressants are associated with a range of side effects that typically do not indicate a safety concern nor predict poor response. Patients are often reassured also to learn about the availability of strategies to address most side effects including dose changes, pharmacological antidotes, and the option to switch to other medications.

Some clinicians are reluctant to discuss side effects in advance because of a concern that it will make patients anxious and may magnify side effect concerns. The literature offers some support of this in a naturalistic study showing that patients who recalled being informed of potential adverse events by their physicians were 55% more likely to report experiencing mild or moderate adverse effects.¹⁰ Although these patients were more likely to report side effects, this same study, as well as a naturalistic study done by Bull et al,² found that discussing adverse effects with patients during treatment was associated with the same or less premature discon-

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tinuation and with a higher rate of switching medications. Switching medications in this instance may represent a positive alternative to discontinuing treatment.

Nondrug therapy

Other successful techniques that have been shown to improve patient adherence to medication include the use of cognitive behavioral therapy and the participation in other concurrent nondrug therapy,¹⁰ particularly when care is closely coordinated between the clinician prescribing medication and the clinician providing psychotherapy when these roles are separate. In another area of medical treatment, Safren et al^{59,60} have shown that in HIV-positive patients, an intervention called Life-Steps, which is a single-session intervention utilizing cognitive-behavioral, motivational interviewing, and problem-solving techniques, improves adherence to HIV antiretroviral therapy. Further study should be directed at specific psychotherapeutic interventions similar to these that support treatment adherence in the pharmacotherapy of depression.

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Conclusion

Antidepressant side effects are a common clinical challenge, often jeopardizing treatment adherence and quality of life. Physicians may underestimate the prevalence of side effects and may be reticent to address them proactively out of a mistaken concern that their impact will be magnified. The successful management of side effects begins with adequate communication and patient education prior to and throughout treatment with antidepressants. In addition, it involves thoughtful differentiation of treatment-emergent side effects from residual depressive symptoms, relapse and recurrence, discontinuation related adverse events, and intercurrent general medical problems. Finally, optimal management of side effects involves drawing upon a full array of strategies including dose reduction, changes in the timing of doses or the drug preparation, behavioral strategies, pharmacological antidotes, and willingness to consider switching to other agents. Sound and resourceful management of side effects is an important component in achieving depressive remission and enhancing patient safety and quality of life. □

Buscando la respuesta óptima: comprensión y manejo de los efectos secundarios de los antidepresivos

En las últimas dos décadas la seguridad y tolerabilidad de los antidepresivos ha mejorado considerablemente. Sin embargo, todavía los efectos secundarios de los antidepresivos son frecuentes y problemáticos. La mayoría de los pacientes tratados con los medicamentos actuales experimentan uno o más efectos secundarios significativos. Estos efectos secundarios a menudo crean barreras para alcanzar la remisión de la depresión, al igual que para prevenir recaídas y recurrencias. Los clínicos tienden a subestimar la prevalencia de efectos secundarios y hasta un cuarto de los pacientes discontinúa los antidepresivos por tolerar mal dichos efectos; otros pueden continuar la terapia antidepresiva, pero experimentan una disminución en la calidad de vida relacionada con los molestos efectos secundarios. Este artículo revisa la prevalencia de efectos secundarios, el impacto de ellos en la adherencia al tratamiento y temas metodológicos que incluyen el desafío de distinguir los efectos secundarios de los síntomas depresivos residuales, los efectos de la discontinuación y problemas médicos generales. Además se hace referencia a los efectos secundarios más comunes como la disfunción sexual, problemas gastrointestinales, alteraciones del sueño, apatía y fatiga, y se ofrecen estrategias para el manejo que pueden ayudar a los pacientes a obtener una respuesta óptima a la farmacoterapia.

Vers une réponse optimale : compréhension et prise en charge des effets secondaires des antidépresseurs

L'innocuité et la tolérance des antidépresseurs ont été considérablement améliorées au cours de ces vingt dernières années. Leurs effets secondaires restent néanmoins courants et source de problèmes. La plupart des patients traités par les molécules actuelles souffrent d'un ou plusieurs effets secondaires gênants. Ceux-ci empêchent souvent l'obtention d'une rémission de la dépression ou de la prévention d'une récurrence ou d'une rechute. Les médecins ont tendance à sous-estimer la prévalence des effets secondaires et jusqu'à un quart des patients arrêtent leur traitement antidépresseur car ils ne tolèrent pas ces effets gênants ; les autres continuent leur traitement mais leur qualité de vie en est diminuée. Cet article passe en revue la prévalence des effets secondaires, leur impact sur l'observance du traitement et les questions méthodologiques comme celle de distinguer les effets secondaires des symptômes dépressifs résiduels, des effets dus à l'interruption du traitement et des affections médicales générales. De plus, nous abordons les effets secondaires les plus courants comme les troubles sexuels, gastro-intestinaux, les perturbations du sommeil, l'apathie et la fatigue et nous proposons des stratégies de prise en charge afin d'aider les patients à obtenir une réponse optimale au traitement médicamenteux.

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Translational research

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Treatment of affective illness – depression

Basic principles of prescribing in depression

- Discuss with the patient choice of drug and utility/availability of other, non-pharmacological treatments.
- Discuss with the patient likely outcomes, such as gradual relief from depressive symptoms over several weeks.
- Prescribe a dose of antidepressant (after titration, if necessary) that is likely to be effective.
- For a single episode, continue treatment for at least 4–6 months after resolution of symptoms (multiple episodes may require longer).
- Withdraw antidepressants gradually; always inform patients of the risk and nature of discontinuation symptoms.

Official guidance on the treatment of depression

NICE guidelines¹ – a summary

- Antidepressants are not recommended in mild depression – watchful waiting, problem-solving and exercise are preferred.
- When an antidepressant is prescribed, a generic SSRI is recommended.
- All patients should be informed about the withdrawal effects of antidepressants.
- For severe or resistant depression a combination of antidepressant and CBT is recommended.
- Patients with two prior episodes and functional impairment should be treated for at least 2 years.

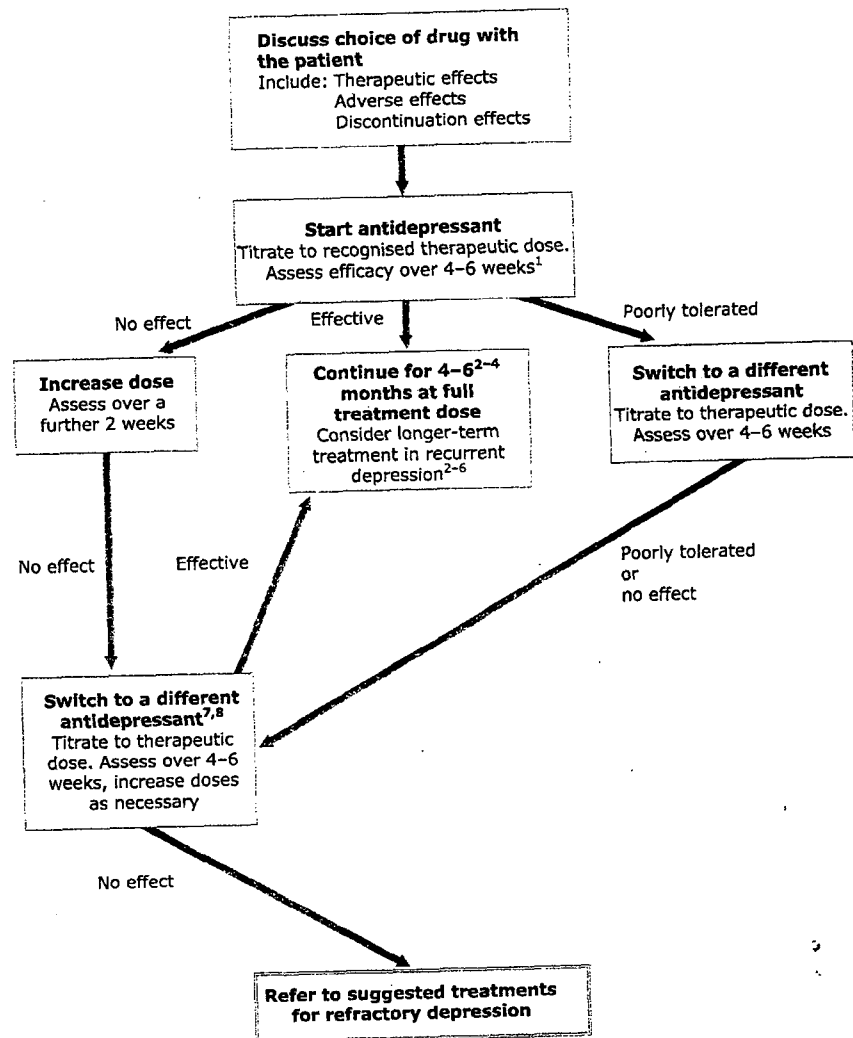
MHRA/CSM Expert Working Group on SSRIs² – a summary

- Use the lowest possible dose.
- Monitor closely in early stages for restlessness, agitation and suicidality. This is particularly important in young people (<30 years).
- Doses should be tapered gradually on stopping.
- Venlafaxine use was originally restricted but this guidance has now been partly reversed (venlafaxine is probably not cardiotoxic^{3,4}, but has a less favourable profile in overdose than SSRIs) (see page 228).

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Drug treatment of depression



Notes

- Tools such as the Montgomery–Asberg Depression Rating Scale⁹ and the Hamilton Depression Rating Scale¹⁰ are recommended to assess drug effect.
- Switching between drug classes in cases of poor tolerability is not well supported by published studies but has a strong theoretical basis. In cases of

Anxiety spectrum disorders

Anxiety is a normal emotion that is experienced by everyone at some time. Symptoms can be psychological, physical, or a mixture of both. Intervention is required when symptoms become disabling.

There are several disorders within the overall spectrum of anxiety disorders, each with its own characteristic symptoms. These are outlined briefly in the table below. Anxiety disorders can occur on their own, be part of other psychiatric disorders (particularly depression), be a consequence of physical illness such as thyrotoxicosis or be drug-induced (e.g. by caffeine)¹. Co-morbidity with other psychiatric disorders is very common.

Anxiety spectrum disorders tend to be chronic and treatment is often only partially successful.

Benzodiazepines

Benzodiazepines provide rapid symptomatic relief from acute anxiety states. All guidelines and consensus statements recommend that this group of drugs should only be used to treat anxiety that is severe, disabling, or subjecting the individual to extreme distress. Because of their potential to cause physical dependence and withdrawal symptoms, these drugs should be used at the lowest effective dose for the shortest period of time (maximum 4 weeks), while medium/long-term treatment strategies are put in place. For the majority of patients these recommendations are sensible and should be adhered to. A very small number of patients with severely disabling anxiety may benefit from long-term treatment with a benzodiazepine and these patients should not be denied treatment². NICE recommends that benzodiazepines should not be used to treat panic disorder³. They should be used with care in post-traumatic stress disorder (PTSD)⁴.

Depression &
anxiety

SSRI – dose and duration of treatment

When used to treat generalised anxiety disorder (GAD), SSRIs should initially be prescribed at half the normal starting dose for the treatment of depression and the dose titrated upwards into the normal antidepressant dosage range as tolerated (initial worsening of anxiety may be seen when treatment is started⁵). Response is usually seen within 6 weeks and continues to increase over time⁶. The optimal duration of treatment has not been determined but should be at least 6 months⁷. Effective treatment of GAD may prevent the development of major depression⁸.

When used to treat **panic disorder**, the same starting dose and dosage titration as in GAD should be used. Doses of clomipramine⁹, citalopram¹⁰ and sertraline¹¹ towards the bottom of the antidepressant range give the best balance between efficacy and side-effects, whereas higher doses of paroxetine (40 mg and above) may be required¹². Higher doses may be effective when standard doses have failed. Onset of action may be as long as 6 weeks.

Women may respond better to SSRIs than men¹³. There is some evidence that augmentation with clonazepam leads to a more rapid response (but not a greater magnitude of response overall)^{12,14}. The optimal duration of treatment is unknown, but should be at least 8 months¹⁵, with some authors recommending up to 18 months¹⁶. Less than 50% of patients are likely to remain well after medication is withdrawn¹⁶.

Lower starting doses are also required in **PTSD**, with high doses (e.g. fluoxetine 60 mg) often being required for full effect. Response is usually seen within 8 weeks, but can take up to 12 weeks¹⁶. Treatment should be continued for at least 6 months and probably longer¹⁷⁻¹⁹.

Although the doses of SSRIs licensed for the treatment of obsessive compulsive disorder (**OCD**) are higher than those licensed for the treatment of depression (e.g. fluoxetine 60 mg, paroxetine 40-60 mg), lower (standard antidepressant) doses may be effective, particularly for maintenance treatment^{20,21}. Initial response is usually slower to emerge than in depression (can take 10-12 weeks). The relapse rate in patients who continue treatment for 2 years is half that of those who stop treatment after initial response (25-40% vs 80%)^{22,23}.

Body dysmorphic disorder (**BDD**) should be treated initially with CBT. If symptoms are moderate-severe, adding an SSRI may improve outcome²⁴. Buspirone may usefully augment the SSRI²⁴.

Standard antidepressant starting doses are well tolerated in **social phobia**²⁵⁻²⁷, and upward-dosage titration may benefit some patients but is not always required. Response is usually seen within 8 weeks and treatment should be continued for at least a year and probably longer²⁸.

All patients treated with SSRIs should be monitored for the development of akathisia, increased anxiety and the emergence of suicidal ideation; the risk is thought to be greatest in those <30 years, those with co-morbid depression and those already known to be at higher risk of suicide²⁴.

SSRIs should not be stopped abruptly, as patients with anxiety spectrum disorders are particularly sensitive to discontinuation symptoms (see page 240). The dose should be titrated down as tolerated over several weeks to months.

Psychological approaches

There is good evidence to support the efficacy of some psychological interventions in anxiety spectrum disorders. Examples include exposure therapy in OCD and social phobia. Initial drug therapy may be required to help the patient become more receptive to psychological input, and some studies suggest that optimal outcome is achieved by combining psychological and drug therapies^{1,3}.

A discussion of the evidence base for psychological interventions is outside the scope of these guidelines. Further information can be found at

Vortioxetine: A New Antidepressant Choice in the United States

Christoph U. Correll, MD | October 02, 2013

A New Multimodal Antidepressant

On September 30, 2013, a new antidepressant, vortioxetine (Brintellix™), produced and comarketed by Lundbeck and Takeda, was approved by the US Food and Drug Administration. The recommended starting dose is 10 mg orally once daily, taken at any time. The dose should then be increased to 20 mg/day, as tolerated, with consideration being given to lowering the dose to 5 mg/day for patients who do not tolerate higher doses. When a new medication is approved, several questions arise for clinicians: How does this medication differ from existing agents that are available to treat the same condition? What is the efficacy and tolerability signature of this new drug? Will certain patients or patient groups benefit most from this new treatment option? In essence, will this medication be an advance, and when and for whom should I prescribe it? These questions are particularly relevant for the treatment of depression because many antidepressant agents targeting monoamine receptors are already available, many of which are generic.

Despite the already wide availability of antidepressants, there is a need for new treatment options. Depression is among the most common psychiatric conditions, treatment response is heterogeneous, and a considerable number of patients benefit only partially from currently available treatments.^[1]

The discovery of the tricyclic antidepressants and the monoamine oxidase inhibitors was followed by the development and approval of several new agents. These include selective serotonin-reuptake inhibitors (SSRIs), serotonin-noradrenaline reuptake inhibitors (SNRIs), and medications such as bupropion, mirtazapine, and certain second-generation antipsychotics that stimulate or block different monoamine receptors. Furthermore, in Europe, agomelatine, a melatonin receptor agonist, has been approved.^[2] Several drugs with potentially novel mechanisms of action have been tested, most of which have failed.^[3,4] A notable exception is the current focus on ketamine and ketamine-like N-methyl-D-aspartate receptor (NMDA) antagonists, which seem to hold promise.^[5] Thus, antidepressants with novel and/or multimodal mechanisms of action are needed.

Vortioxetine

Mechanisms of Action

Vortioxetine is considered a new multimodal antidepressant. It has demonstrated antagonistic properties at 5-HT_{3A} and 5-HT₇ receptors, partial agonistic properties at 5-HT_{1B} receptors, agonistic properties at 5-HT_{1A} receptors, and potent inhibition of the serotonin reuptake transporter.^[6] Of note, preclinical data suggest that these multiple (and in combination) unique effects on numerous serotonin receptors result in regional increases in noradrenaline and dopamine^[7] as well as glutamatergic transmission.^[8]

Pharmacokinetics

Vortioxetine is metabolized by several different liver enzymes (eg, CYP2D6, CYP2C9, CYP3A4/5, CYP2A6, and CYP2C19), suggesting that serum levels should be relatively unaffected by commonly used medications metabolized predominantly by these pathways.^[9] Vortioxetine has a linear dose-response relationship and its half-life is about 57 hours,^[10] suggesting that rebound and withdrawal phenomena after missing doses or stopping the medication are unlikely.

Efficacy

Data from 6 of 8 short-term, placebo-controlled studies in the initial pivotal program, conducted internationally, have shown significant efficacy of vortioxetine in a dose range from 5 to 20 mg/day but most consistently at doses of 15-20 mg/day.^[11-14] Two low-dose studies, (2.5 mg/day and 5 mg/day of vortioxetine) did not separate

the efficacy of the drug from placebo.^[15,16] Furthermore, acute antidepressant efficacy was demonstrated in an elderly population (mean age, 70.6 years).^[17]

Long-term efficacy of vortioxetine has also been established. In a placebo-controlled, relapse-prevention study, patients aged 18-75 years with a current major depressive disorder episode lasting 4 or more weeks received 12-week, open-label vortioxetine at 5 or 10 mg/day. Altogether, 396 patients in remission, with Montgomery-Åsberg Depression Rating Scale (MADRS) scores of ≤ 10 at weeks 10 and 12, were assigned to double-blind treatment with either placebo or vortioxetine at a fixed dose from week 8 onward.^[18] In the primary analysis of time to relapse, vortioxetine was significantly superior to placebo, with a hazard ratio of 2.01 (95% confidence interval, 1.26-3.21; $P = .0035$). Relapse rates were 13% in the vortioxetine group compared with 26% in the placebo group, resulting in a number-needed-to-treat of 8.

Furthermore, open-label, 52-week data showed maintenance of the acutely gained benefits.^[19] By the end of the 52-week open study, using observed case analyses, the proportion of responders increased substantially, from 63% to 94%, as did the number of patients in remission; the proportion of patients with MADRS scores ≤ 10 increased from 42% to 83%. Only 9.7% of 226 patients in remission at the start of the open-label study, who received 8 weeks of acute treatment with vortioxetine, experienced a relapse (defined as a MADRS score ≥ 22).^[18]

Although endpoint changes in depression ratings in earlier trials were numerically lower than with the active comparator duloxetine,^[17,20,21] or were similar to venlafaxine,^[12] these studies were conducted in unselected patient populations and were not powered for a comparison with the active drug that was used for assay sensitivity of the trial. An exception is the REVIVE study^[22] that compared the efficacy of vortioxetine with the most recently approved novel antidepressant in Europe, agomelatine, in a well-powered, head-to-head trial. Of note, the patients were non- or partial responders with a history of at least 6 weeks of treatment with an SSRI or SNRI who were then abruptly switched to 12 weeks of randomized treatment with either vortioxetine (10-20 mg/day; $n = 253$) or agomelatine (25-50 mg/day; $n = 243$). In this "out of class" switch strategy for patients with insufficient response to first-line antidepressants, vortioxetine led to significantly greater improvement in MADRS scores at 8 weeks compared with agomelatine (-2.2 at 8 weeks using mixed-models analyses and -3.1 points using last-observation-carried-forward analyses), with similar effects at week 12. Response and remission rates were also higher with vortioxetine than with agomelatine (response: 61.5% vs 47.3% at week 8 and 69.8% vs 56.0% at week 12; remission: 40.5% vs 29.5% at week 8 and 55.2% vs 39.4% at week 12). Furthermore, vortioxetine separated from agomelatine on key secondary outcomes, including anxiety, the Clinical Global Impressions Severity and Improvement scores, and the Sheehan Disability Scale.^[22]

Finally, on the basis of mechanism of action, vortioxetine is being studied for potentially beneficial effects on cognition. Initial data on the potentially procognitive effects of vortioxetine, independent of the drug's effects on symptoms of depression, have been generated in elderly patients with major depressive disorder.^[17] Other studies with cognition as a primary outcome are ongoing.

Safety Data

The most common adverse effects of vortioxetine across multiple studies were nausea, diarrhea, dry mouth, hyperhidrosis, and headache.^[11,15,16,19] For example, in a 6-week study, the most common adverse effects in the vortioxetine and placebo groups were nausea (19.1% and 9.4%), headache (17.1% and 15.1%), and diarrhea (11.4% and 7.0%).^[16] The potential benefits of vortioxetine include low rates of sedation/somnolence and insomnia, low weight gain in acute and 1-year studies,^[23] and possibly improved tolerability with respect to sexual side effects compared with SSRIs. In the aforementioned head-to-head study with agomelatine, the number of patients randomly assigned to vortioxetine or agomelatine with at least 1 adverse event were 54.2% vs 52.5% at 12 weeks.^[22] More patients on vortioxetine than agomelatine had nausea or vomiting (16.2% vs 9.1%), whereas agomelatine was associated with more dizziness (11.6% vs 7.1%) and sedation (7.9% vs 4.0%).

Comment

After some negative studies, primarily using low doses and conducted in the United States, the overall data clearly support the efficacy and safety of vortioxetine in adults with major depressive disorder. As a result of the diverse and partially novel mechanisms of action of vortioxetine, this new multimodal antidepressant holds promise for patients who have not benefited from currently available, first-line treatment options for depression. Although phase 2 trials that included duloxetine and paroxetine as active comparators did not suggest superior efficacy, it must be recognized that patients enrolled in double-blind, placebo-controlled trials are not representative of patients seen and treated in clinical practice. Moreover, patients were not selected for insufficient response to a first-line antidepressant. In this context, the study comparing vortioxetine with agomelatine, another novel mechanism antidepressant but currently approved in Europe only, requires replication with an antidepressant approved in the United States.

Future studies should examine whether vortioxetine has more robust efficacy in certain patient subgroups, including treatment-nonresponsive/resistant patients and those with comorbid cognitive problems. Moreover, its safety profile indicates that vortioxetine may be particularly beneficial for patients who experienced weight gain, sedation, and/or sexual side effects while on other antidepressants. Nevertheless, it is acknowledged that pharmacodynamic and phase 1-3 data only go so far. Clearly, the broader picture of vortioxetine's clinical utility and place in the treatment of patients with depression will need to be established through its clinical use after approval and ongoing and future phase 4 trials.

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