



No. 06-021584- -00005-0000

Fecha: 2007-12-27 15:34:04 Dep. 2020 NUECREACION
Tra 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 400 OPOSIOBSERVTER Folios: 106

FORMULARIO ÚNICO DE OPOSICIÓN

①

OPOSICIÓN A:

- | | |
|--|--|
| ☒ Patente de Invención. | ☐ Marca Colectiva. |
| ☐ Patente de Modelo de Utilidad. | ☐ Marca de Certificación. |
| ☐ Diseño Industrial. | ☐ Lema Comercial. |
| ☐ Esquema de Trazado para Circuitos Integrados. | |
| ☐ Marcas de Productos o Servicios. | |

②

SOLICITUD
PUBLICADA

Numero del expediente: 06-021584

Solicitante: H. LUNDBECK A/S

Apoderado: EMILIO FERRERO

Título de la nueva creación o denominación del signo: "COMBINACIÓN DE UN INHIBIDOR DE RECAPTACION DE SEROTONINA Y LOXAPINA".

Gaceta: 580

③ OPOSICIÓN PRESENTADA POR:

SOLICITANTE	Nombre: PROCAPS S.A	IDENTIFICACIÓN C.C. ☐ NIT ☒ C.E. ☐ Otro ☐ Cual _____ Número <u>890.106.527-5</u>
	Dirección: CALLE 80 No. 78B -201 Nacionalidad o Domicilio: COLOMBIA Lugar de Constitución: BARRANQUILLA Teléfono: (571)3719900 Fax: (571)3730818 E-mail: _____	
REPRESENTANTE O APODERADO	Nombre: ELIANA ISAURA MORENO BOHORQUEZ Dirección: CARRERA 13 No. 119-95 OF 104 Teléfono: (571)2131213 Fax: (571)6121979 E-mail: negocios@optimum-co.com	IDENTIFICACIÓN C.C. ☐ NIT ☒ C.E. ☐ Otro ☐ Cual _____ Número <u>51.975.664</u> TP <u>83823</u>

④ FUNDAMENTOS DE LA OPOSICIÓN:

Art.14, 16, 18, 20 y 30 de la Decisión 486 de la CAN

Causal: No cumple con los requisitos de patentabilidad.

Signo opositor: _____

Justificación: _____

La presente solicitud no cumple con los requisitos de patentabilidad dado que lo revelado, ya se encontraba en el estado de la técnica o es posible derivarlo de la misma tal y como se demostrará en el capítulo "Fundamento de Hechos".

⑤ Comprobante de pago No. _____

Fecha _____

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⑥ ANEXOS

- ☒ Comprobante de pago de la tasa.
- ☒ Poderes, si fuere el caso.
- ☒ Pruebas de los fundamentos de la oposición.
- ☐ Documentos que acrediten el legítimo interés, si fuere el caso.
- ☒ Documento que acredita la existencia y representación legal de las partes, cuando sean personas jurídicas.

⑦

NOMBRE: ELIANA ISAURA MORENO BOHORQUEZ

FIRMA: _____

C.C. 51.975.664

TP. 83823

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 06-021584- -00005-0000

Fecha: 2007-12-27 15:34:04 Dep. 2020 NUECREACION
Tra. 11 PATENTE/II Eva: 378 FASENACIONALI
Act. 400 OP05/OBSERVTER Folios: 106

RECIBO OFICIAL DE CAJA : 07 - 105,004
FECHA : DICIEMBRE 27 DE 2007

***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	Vr. PAGO
GYNOPHARM S.A.	CONSIGNACION	BANCO POPULAR	050-00110-6	71247173	18/12/2007	3,584,000.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO	
1	50005-01-04	PRESENTACION DE OBSERVACIONES	12 MARCAS Y LEMAS COMERCIALES	256,000.00
			TOTAL :	\$ 256,000.00

SON: DOSCIENTOS CINCUENTA Y SEIS MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

Señora Jefe,

DIVISIÓN DE NUEVAS CREACIONES

Superintendencia de Industria y Comercio

E. S. D.

Referencia : Expediente N° 06021584
 Asunto : Oposición a la solicitud de patente de Invención titulada
 “COMBINACION DE UN INHIBIDOR DE
 RECAPTACION DE SEROTONINA Y LOXAPINA”
 Solicitante : H LUNDBECK A/S.
 Opositora : PROCAPS S.A.

Publicada en la Gaceta de la Propiedad Industrial

N° 580 del 28 de septiembre de 2007

Yo, *ELIANA ISAURA MORENO BOHORQUEZ*, abogada en ejercicio, identificada como aparece al pie de su firma, con tarjeta profesional No. 83823 del Consejo Superior de la Judicatura, en mi condición de apoderada de la sociedad **PROCAPS S.A.** conformada bajo las leyes de la República de Colombia y domiciliada en la ciudad de Barranquilla, Colombia, atentamente manifiesto que estando dentro del término de ley y por orden expresa de mi representada, presento oposición a la concesión del registro de la Patente de Invención titulada “COMBINACION DE UN INHIBIDOR DE RECAPTACION DE SEROTONINA Y LOXAPINA”, cuyo titular es H LUNDBECK A/S, y pido a Usted declarar fundada esta oposición y en consecuencia negar el registro de la patente solicitada.

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1. INTERÉS PARA ACTUAR

Conforme a lo dispuesto en el artículo 42 de la Decisión 486 de 2000 de la CAN, estando dentro del término estipulado por la ley, manifiesto el legítimo interés de nuestra representada para oponerse al registro de la patente de la referencia, atendiendo a que la solicitud pretendida no cumple con los requisitos dispuestos en la ley como se analizará más adelante y de ser concedida afectaría directamente la comercialización de algunos productos de mi representada, que contienen, en particular inhibidores de Serotonina y Loxapina. Por lo tanto, solicito respetuosamente a ese Despacho se sirva tener en cuenta la presente oposición dentro del trámite administrativo que se surte en esta Superintendencia.

2. FUNDAMENTOS DE HECHOS

2.1. La solicitud objeto de la presente fue presentada el 3 de marzo de 2006, reivindicando prioridad bajo las solicitudes DK20030001270 del 20030904; y, US20030500809P del 20030904, y fue publicada en Colombia, en la Gaceta de la Propiedad Industrial N° 580 del 28 de septiembre de 2007 página 431 y N° publicación 419, cuya publicación internacional corresponde a la WO2005023243 del 2005-03-17.

2.2. La solicitud colombiana **06-021584** objeto de la presente oposición, se refiere a una composición farmacéutica que comprende loxapina o una sal farmacéuticamente aceptable del mismo y un compuesto, el cual es inhibidor de recaptación de serotonina, el cual provoca una elevación en la concentración de serotonina extracelular, la cual opcionalmente presenta portadores o diluyentes

farmacéuticamente aceptables, donde el inhibidor de recaptación de serotonina se selecciona de citalopram, escitalopram, fluoxetina, sertralina, paroxetina, fluvoxamina, venlafaxina, dapoxetina, nefazodona, imipramina, femoxetina y clomipramina, en donde el inhibidor de recaptación de serotonina es un inhibidor selectivo de recaptación de serotonina, la cual está adaptada para administración simultánea de los ingredientes activos, en donde los ingredientes activos están contenidos en la misma forma de dosificación unitaria, en donde está adaptada para administración secuencial de los ingredientes activos.

2.3. Ahora bien, con base en el artículo 14 de la Decisión 486 de la CAN consagra lo siguiente: *“Los países miembros otorgarán patentes para las invenciones, sean de producto o procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial”*. Así las cosas, las invenciones objeto de patente deben ser nuevas y tener nivel inventivo. Bien, pues antes de la fecha de prioridad de esta solicitud se encuentran los siguientes documentos que afecta la patentabilidad de la presente solicitud:

- D1: WO0151041 publicada el 19 de julio de 2001.
- D2: US2002151543 publicada el 17 de octubre de 2002.
- D3: US2003130266 publicada el 10 de julio de 2003.
- D4: EP0958824 publicada el 24 de noviembre de 1999.

2.4. Ahora bien, el documento D1, particularmente revela una composición farmacéutica que comprende una forma osmótica de liberación controlada que contiene venlafaxina en el núcleo en combinación con un agente antipsicótico de rápida liberación en la cubierta. Esta forma, según el documento D1, es útil para el tratamiento de la ansiedad, de depresión o psicosis. Con base en las reivindicaciones, el documento D1 revela con anterioridad una forma osmótica para la entrega de

venlafaxina y un agente antipsicótico comprendiendo: un núcleo que comprende una cantidad terapéuticamente eficaz de VFX y al menos un agente osmótico u osmopolimero; una membrana semipermeable que rodea el núcleo; y una cubierta externa que comprende una cantidad terapéuticamente eficaz de un agente antipsicótico; en el que el núcleo proporciona una liberación controlada de VFX, y al menos el 80 % del VFX es liberado dentro de 13 horas después de que la exposición del dispositivo osmótico a una solución acuosa, y la cubierta proporciona una rápida liberación del agente antipsicótico, y al menos el 75 % del agente antipsicótico es liberado dentro de 1 hora después de la exposición de la forma osmótica a una solución acuosa. Así, las cosas, la presente solicitud no es novedosa pues lo revelado ya se encontraba en el estado de la técnica, particularmente en el documento D1.

2.5. Por su parte, el documento D2, revela una composición farmacéutica que comprende loxapina y (R)-fluoxetina para el tratamiento de la psicosis. Particularmente, este documento ya evidencia estudios y soluciones similares a la propuesta en la presente solicitud objeto de oposición, tal como el indicado en el párrafo 0039, que revela las enfermedades o los trastornos pueden ser tratados o prevenidos usando la R (-) fluoxetina y una benzodiazepina. En las reivindicaciones, este documento D2 revela un método para tratar una enfermedad psicótica o psiquiátrica en un mamífero que comprende la administración de una cantidad eficaz de R (-) fluoxetine o una sal farmacéuticamente aceptable, considerablemente sin su S (+) el estereoisómero, y una cantidad eficaz de un compuesto biológicamente activo tricíclico antipsicótico. Por lo tanto, este documento objeto de oposición a la luz del documento D2 carece evidentemente de NOVEDAD.

2.6. Ahora bien, el documento D3, también ofrece una solución similar a la aquí propuesta dado que se revela con anterioridad una combinación farmacéutica de un inhibidor de SSR y un antagonista receptor de serotonina. En esta anterioridad

se revelan varios ejemplos que ello, que incluyen una cantidad de loxapina. De hecho en la cláusula 13, revela un método de tratamiento en trastornos respiratorios relacionados con el sueño que comprende administrar a un paciente una cantidad eficaz de al menos un antagonista receptor de serotonina en su base libre o en su forma de cuaternaria seleccionada del grupo que consiste en zatosetrona, tropisetrona, dolasetrona, hidrodolasetrona, mezcaltina, oxetorona, homoclorciclizina, perlapina, loxapina, olanzapina, calpromazina, haloperidol, (+) ondansetrona, cisaprida, norcisaprida, (+) cisaprida, (-) cisaprida, (+) norcisaprida, (-) norcisaprida, desmetilolanzapina, 2-hidroximetilolanzapina, 1-3-oxime (2-fluorofenil) (4-hidroxi aminoetil)-prop-2-en-1-one-O-(2-dimetil aminoetil); y en su forma de cuaternaria seleccionada del grupo que consiste en ondansetrona, ketanserina, risperidona, cyproheptadina, clozapina, methysergida, granisetrona, mianserina, ritanserina, cinanserina, LY-53,857, metergolina, LY-278,584, methiothepin, p-NPPL, YAYA 190, piperazine, SB-206553, SDZ-205,557, 3-tropanil-indole-3-20 carboxilato, y 3-tropanil-indol-3-carboxilato metiodida; y mezclas de los mismo; y una cantidad eficaz de un inhibidor selectivo serotonina. Por lo tanto, a los ojos de este documento D3, la presente solicitud también carece evidentemente de novedad.

2.7.El documento D4, revela por su parte una composición farmacéutica adaptada para el tratamiento de un paciente que sufre de depresión que incluye ingredientes activos en una combinación de antipsicóticos y un inhibidor de nueva respuesta serotonina. Como tal, las reivindicaciones de este documento D4, revelan con anterioridad un método para tratar un paciente que sufre de depresión que comprende administrar al paciente una cantidad eficaz de un primer componente de un antipsicótico atípico, en la combinación con una cantidad eficaz de un segundo componente que es un inhibidor de serotonina. De esta manera, este

documento objeto de oposición a la luz del documento D4 también carece evidentemente de NOVEDAD.

2.8. En consecuencia y de acuerdo a lo descrito anteriormente, se deriva que la solicitud colombiana **06-021584** no puede pretender un monopolio por patente toda vez que lo que pretende no cumple con los requisitos necesarios para su protección.

2.9. Que por consiguiente, respecto a la solicitud pretendida se tiene que:

2.9.1. **CARECE DE NOVEDAD**: Según la decisión 486 de la Comunidad Andina de Naciones, Artículo 16.- *“Una invención se considerará nueva cuando no está comprendida en el estado de la técnica. El estado de la técnica comprenderá todo lo que haya sido accesible al público por una descripción escrita u oral, utilización, comercialización o cualquier otro medio antes de la fecha de presentación de la solicitud de patente o, en su caso, de la prioridad reconocida.”*. A la fecha de prioridad, 4 de septiembre de 2003 ya era conocido, pues como se demostró, era parte del arte anterior con base en los documentos D1, D2, D3 y D4 una composición farmacéutica que comprende loxapina o una sal farmacéuticamente aceptable del mismo y un compuesto, el cual es inhibidor de recaptación de serotonina, el cual provoca una elevación en la concentración de serotonina extracelular, la cual opcionalmente presenta portadores o diluyentes farmacéuticamente aceptables, en donde los ingredientes activos están contenidos en la misma forma de dosificación unitaria, en donde está adaptada para administración secuencial de los ingredientes activos, sobre el cual busca protección en el capítulo reivindicatorio.

2.10. Dado lo anterior, es posible deducir que la solicitud y lo reivindicado no es objeto de patentabilidad pues es contrario a lo que dicta la Decisión 486 de la Comunidad Andina de Naciones, Artículo 14.- *“Los Países Miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación*

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industrial.". La solicitud pretendida no cumple con los requisitos de patentabilidad, particularmente la NOVEDAD.

2.11. Por todo lo anterior, atentamente solicito a usted que se sirva declarar fundada la presente oposición y negar el registro Patente de invención denominada **“COMBINACION DE UN INHIBIDOR DE RECAPTACION DE SEROTONINA Y LOXAPINA”**, cuyo titular es **H LUNDBECK A/S,,** solicitud Colombiana que apareció publicada en la Gaceta de la Propiedad Industrial N° 580.

3. PRUEBAS

De conformidad con lo dispuesto por las normas vigentes, solicito a usted tener como prueba en este asunto los siguientes:

- D1: WO0151041 publicada el 19 de julio de 2001.
- D2: US2002151543 publicada el 17 de octubre de 2002.
- D3: US2003130266 publicada el 10 de julio de 2003.
- D4: EP0958824 publicada el 24 de noviembre de 1999.

4. FUNDAMENTO DE DERECHO

Fundamento esta observación en las normas legales siguientes:

4.1. Numeral 1 del artículo 586 del Código de Comercio.

4.2. Artículo 42 de la Decisión 486 de la Comisión del Acuerdo de Cartagena.

4.3. En las demás normas concordantes.

5. ANEXOS

Para los efectos correspondientes anexo al presente escrito los siguientes documentos:

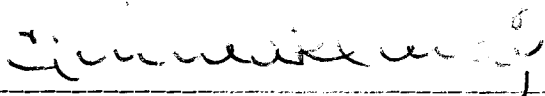
1. Poder para actuar en el presente.
2. Documento que acredita al representante legal de PROCAPS S.A.
3. Recibo de caja del respectivo pago de tasa.
4. Copias de los documentos:

- D1: WO0151041 publicada el 19 de julio de 2001.
- D2: US2002151543 publicada el 17 de octubre de 2002.
- D3: US2003130266 publicada el 10 de julio de 2003.
- D4: EP0958824 publicada el 24 de noviembre de 1999.

6. NOTIFICACIONES

- Para efectos de notificaciones que por disposición del artículo 50 del Decreto 01 de 1984 debe hacer su Despacho, informo que mi representada y la suscrita recibiremos notificaciones en la Secretaría de su Despacho o en mis oficinas situadas en la Carrera 13 N° 119-95, Of. 104 de esta ciudad de Bogotá.

Señor Superintendente,



ELIANA ISAURA MORENO BOHORQUEZ

C.C. 51'975.664 de Bogotá

T.P.A. 83823 del C.S. de la J.



PODER ESPECIAL

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Yo, **WALTER TANAKA TATEKAWA**, mayor de edad y vecino de la ciudad de Barranquilla (Colombia), identificado como aparece al pie de mi firma, quien en el presente documento actúa en calidad de Representante Legal de la sociedad **PROCAPS S.A.** sociedad legalmente constituida y domiciliada en la ciudad de Barranquilla (Colombia), por el presente documento otorgo a la doctora **ELIANA ISAURA MORENO BOHORQUEZ**, abogada en ejercicio, identificada como aparece al pie de su firma, con tarjeta profesional No. 83823 del C.S. de la J., poder especial, amplio y suficiente, para formular oposiciones u observaciones a la solicitud de patente No. **06.021.584**, titulada "**COMBINACION DE UN INHIBIDOR DE RECAPTACION DE SEROTONINA Y LOXAPINA**", cuyo titular es **H LUNDBECK A/S**, publicada en la gaceta No. 580 del 28 de Septiembre de 2007.

Nuestro apoderado queda facultado, de manera expresa, para realizar todo tipo de actos necesarios para llevar a cabo el trámite de la oposición, incluyendo, sin limitación, preparar y presentar solicitudes, hacer declaraciones, pagar tasas, contribuciones e impuestos, recabar los títulos o certificados. Asimismo quedan autorizados para impugnar administrativa y judicialmente todo lo que fuere resuelto en el expediente a que se hace expresa referencia en el presente poder, con todas las facultades generales y específicas que fuera requerido para ella.

De la misma manera, además de las facultades que le confiere la naturaleza del presente mandato, se encuentran facultados para recibir, desistir, transigir, sustituir, y reasumir el presente poder, incoar acciones, interponer recursos y demás facultades conferidas por la ley.

Dado y Firmado en Barranquilla (Colombia) a los 6 días del mes de Diciembre de 2007.

PROCAPS S.A.

WALTER TANAKA TATEKAWA
C.C. N° 16.251.923 de Palmira
Representante Legal

Acepto:

ELIANA ISAURA MORENO BOHORQUEZ
C.C. 51'975.664 de Bogotá
T.P.A. 83823 del C.S. de la J.



***** Pag. 1
C A M A R A D E C O M E R C I O
D E B A R R A N Q U I L L A
09*****

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.

PROCAPS S.A.-----

NIT: 890.106.527-5.

EL SUSCRITO SECRETARIO DE LA CAMARA DE COMERCIO DE BARRANQUILLA, CON FUNDAMENTO EN LAS INSCRIPCIONES DEL REGISTRO MERCANTIL:

C E R T I F I C A

Que por Escritura Pública No. 1,190 del 22 de Julio de 1976, otorgada en la Notaria Tercera de Barranquilla, inscrito(as) en esta Cámara de Comercio, el 28 de Julio de 1976 bajo el No. 6,070 del libro respectivo, fue constituida la sociedad----- limitada denominada "PRODUCTORA DE CAPSULAS DE GELATINAS LIMITADA "PROCAPS LIMITADA".-----

C E R T I F I C A

Que por Escritura Pública No. 1,307 del 28 de Junio de 1979, otorgada en la Notaria Tercera de Barranquilla, inscrito(as) en esta Cámara de Comercio, el 23 de Julio de 1979 bajo el No. 10,039 del libro respectivo, la sociedad antes mencionada----- se transformo en sociedad anonima bajo la denominacion social de "PRODUCTORA DE CAPSULAS DE GELATINA S.A." PROCAPS S.A.".-----

C E R T I F I C A

Que por Escritura Pública No. 3,810 del 31 de Dic/bre de 1980, otorgada en la Notaria Primera de Barranquilla, inscrito(as) en esta Cámara de Comercio, el 30 de Enero de 1981 bajo el No. 12,705 del libro respectivo, la sociedad antes mencionada----- se transformo en sociedad de responsabilidad limitada bajo al razon social de "PRODUCTORA DE CAPSULAS DE GELATINA LIMITADA "PROCAPS LI - MITADA".-----

C E R T I F I C A

Que por Escritura Pública No. 3,755 del 10 de Nov/bre de 1983, otorgada en la Notaria Unica de Soledad, inscrito(as) en esta Cámara de Comercio, el 22 de Nov/bre de 1983 bajo el No. 17,922 del libro respectivo, la sociedad antes mencionada----- se transformo en sociedad anonima bajo la denominacion social de "PRODUCTORA DE CAPSULAS DE GELATINA S.A. "PROCAPS S.A.".-----

C E R T I F I C A

Que por Escritura Pública No. 3,615 del 06 de Dic/bre de 1996, otorgada en la Notaria 2a. de Barranquilla, inscrito(as) en esta Cámara de Comercio, el 20 de Dic/bre de 1996 bajo el No. 67,218 del

***** C O N T I N U A *****



***** Pag. 2
C A M A R A D E C O M E R C I O
D E B A R R A N Q U I L L A
09*****

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.

PROCAPS S.A.-----

NIT: 890.106.527-5.

Direccion para notificaciones judiciales:

CL 80 No 78 B - 201.

De la ciudad de Barranquilla.

C E R T I F I C A

DURACION: El término de duración de la sociedad se fijó hasta el 18 de Agosto de 2073.

C E R T I F I C A

OBJETO SOCIAL: El objeto principal de la sociedad sera: a)-La fabricacion de capsulas y otros productos similares a partir de materiales tales como gelatinas u otros de distinta naturaleza, que puedan ser utilizados como envases o recipientes de productos y sustancias quimicas, farmaceuticas y cosmeticas, para uso y consumo humano y veterinario; b)-La investigacion, desarrollo y fabricacion de toda clase de productos y sustancias quimicas, farmaceuticas y cosmeticas para uso y consumo humano, animal y vegetal; c)-La compra y venta de materias primas, insumos y productos intermedios necesarios para los procesos de fabricacion de sustancias quimicas, farmaceuticas, alimenticias y cosmeticas, asi como la comercializacion interna y externa de los productos terminados, d) La compra, venta, importacion, exportacion y distribucion de toda clase de elementos instrumentales y equipos medicos, quirurgicos, odontologicos, y hospitalarios para la salud humana y animal. e) La compra, venta, exportacion y distribucion de dulces, confites, galletas y todo tipo de golosinas o alimentos para el consumo humano. f) Actuar como representante o agente de personas naturales y juridicas, nacionales y extranjeras en la realizacion de operaciones o transacciones relacionadas con la industria farmaceutica y en especial con cualquiera de las actividades descritas en los literales a), b), c). d) y e) antes descritos; g) Prestar los servicios de asesoria y consultoria en las areas administrativas, de mercadeo, analisis clinico, asistencia tecnica, investigacion, costos y produccion, exportaciones, importaciones, ventas, relacionadas con iguales o similares actividades a las que constituyen el objeto de PROCAPS S.A., asi como los de publicidad y promocion de productos quimicos, cosmeticos y farmaceuticos para uso humano, animal o industrial; h)-Adquirir, operar, administrar y explotar, a cualquier titulo, empresa o establecimientos dedicados a la investigacion, desarrollo, fabricacion o comercializacion de productos quimicos, farmaceuticos, hospitalarios o cosmeticos. En desarrollo de su objeto principal, la sociedad podra tomar interes social como accionista,

***** C O N T I N U A *****



CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.

PROCAPS S.A.-----
NIT: 890.106.527-5.

en pesos colombianos a doscientos cincuenta mil dolares de los Estados Unidos de America (US\$250.000), liquidados a la tasa de cambio representativa del mercado vigente el dia en que se surta la transacion o celebracion del acto. Las demas funciones que le correspondan como Representante Legal por disposicion de la ley, de estos estatutos o de la Junta Directiva. El Presidente tendra un suplente, designado por la Junta Directiva, quien reemplazara al Presidente en sus faltas temporales, absolutas o meramente accidentales, con entidades facultades y sin que sea necesario para ello acreditar la ausencia del principal. La sociedad tendra un Vicepresidente designado por la Junta Directiva, quien tambien ejercera la representacion legal de la sociedad, pudiendo ejercerla conjunta o separadamente con el Presidente. El vicepresidente tendra las siguientes facultades entre otras. Ejecutar dentro de su competencia las decisiones de la Asamblea General de Accionistas, de la Junta Directiva y del Presidente. Ejercer la representacion legal de la sociedad en todos los actos y contratos que se requieran para el desarrollo del objeto social, de conformidad con lo previsto en las leyes y en los presentes estatutos. Constituir apoderados judiciales y extrajudiciales, recibir notificaciones, absolver interrogatorios de parte, confesar obligaciones de la sociedad, transigir, desistir y allanar a la sociedad en cualquier asunto judicial. Aprobar y celebrar en nombre de la sociedad todo acto o contrato cuya cuantia sea igual o inferior al equivalente en pesos colombianos a ciento cincuenta mil dolares de los Estados Unidos de America (US\$150.000), liquidados a la tasa de cambio representativa del mercado vigente el dia en que se surta la aprobacion o celebracion del acto, siempre que no se trate de enajenar bienes inmuebles o cualquier otro activo fijo de la sociedad, inclusive de naturaleza muebles, acciones, cuotas o partes de interes inversiones y todo tipo de derechos de la sociedad, o de constituir gravámenes sobre cualquiera de los anteriores, facultades que radican exclusiva y privativamente en cabeza del Presidente. Las demas funciones que le corresponda como Representante legal por disposicion de la ley, de estos estatutos o de la Junta Directiva. El Vicepresidente tendra (1) suplente, designado por la Junta Directiva, quien lo reemplazara conjunta o separadamente en sus faltas temporales, absolutas o meramente accidentales, con identicas facultades y sin que sea necesario para ello acreditar la ausencia del principal. La sociedad tendra un (1) Gerente General, con su respectivo Suplente, designados por la Junta Directiva. El Suplente reemplazara al Gerente General, en sus faltas temporales, absolutas o meramente accidentales, quien junto con el gerente general, llevaran la representacion legal de la sociedad, con identicas facultades, pudiendolas ejercer conjunta o separadamente con el Presidente y Vicepresidente, con identicas facultades

***** C O N T I N U A *****



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C A M A R A D E C O M E R C I O
D E B A R R A N Q U I L L A
09*****

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.

PROCAPS S.A.-----
NIT: 890.106.527-5.

Minski Gontovnik Ruben	CC.*****7,463,982
Suplente del Presidente	
Minski Minski Abraham	CC.*****802,575
Vicepresidente	
Minski Gontovnik Meyer	CC.*****7,461,324
Suplente del vicepresidente	
Minski Gontovnik Jose	CC.*****8,671,834

C E R T I F I C A

Que según Acta No. 11 del 01 de Febrero de 2001 correspondiente a la Junta Directiva en Barranquilla, de la sociedad: PROCAPS S.A. cuya parte pertinente se inscribió en esta Cámara de Comercio, el 12 de Febrero de 2001 bajo el No. 91,273 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre	Identificación
Gerente General.	
Uribe Ochoa Guillermo Luis	CC.*****70,073,754

C E R T I F I C A

Que según Acta No. 406 del 02 de Sep/bre de 2004 correspondiente a la Junta Directiva en Barranquilla, de la sociedad: PROCAPS S.A. cuya parte pertinente se inscribió en esta Cámara de Comercio, el 09 de Sep/bre de 2004 bajo el No. 113,263 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre	Identificación
Suplente del Gerente.	
Tanaka Tatekawa Walter	CC.*****16,251,923

C E R T I F I C A

Que según Acta No. 124 del 29 de Marzo de 1999 correspondiente a la Asamblea de Accionistas en Barranquilla, de la sociedad: PROCAPS S.A. cuya parte pertinente se inscribió en esta Cámara de Comercio, el 04 de Agosto de 1999 bajo el No. 82,226 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre	Identificación
Revisor Fiscal Ppal.	
Vargas Pertuz Ana Isabel	CC.*****32,696,645

C E R T I F I C A

Que según Acta No. 127 del 22 de Marzo de 2000 correspondiente a la Asamblea de Accionistas en Barranquilla, de la sociedad: PROCAPS

***** C O N T I N U A *****



***** Pag. 5
C A M A R A D E C O M E R C I O
D E B A R R A N Q U I L L A
09*****

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.

PROCAPS S.A.-----

NIT: 890.106.527-5.

compensacion de impuestos y recibir los pagos por devoluciones de impuestos, firmar, notificarse y realizar todo acto necesario para cumplir con el mandato encomendado.-----

C E R T I F I C A

Que segun documento privado de fecha 7 de junio de 2000, inscrito en esta Camara de Comercio el 8 de junio de 2000, bajo el No.1.786 del libro respectivo, consta que RUBEN MINSKI GONTOVNIK, C.C. No. 7.463.982 de Barranquilla, actuando como Presidente y Representante Legal de la sociedad PROCAPS S.A, confiere poder especial, amplio y suficiente a KAREN FIGUEROA GARCIA, C.C.No.32.732.070 de Barranquilla, para que en su nombre y representacion de la sociedad suscriba todas declaraciones cambiarias a que este obligada PROCAPS S.A, en el giro normal de sus negocios y operaciones sociales.--

C E R T I F I C A

Que segun Documento Privado del 13 de diciembre del 2.002, inscrito en esta Camara de Comercio el 15 de enero del 2.003 bajo el No.2.290 del libro respectivo, el senor RUBEN MINSKI GONTOVNIK, C.C.No.7.463.982, en calidad de REPRESENTANTE LEGAL, y en condicion de PRESIDENTE de PROCAPS S.A., mediante el presente documento otorgo PODER ESPECIAL al Sr. MARLON TATIS PAREDES, C.C.No.72.176.874, para que en representacion de PROCAPS S.A., suscriba declaraciones, reportes y cualquier tipo de documentos relacionados con tramites o registros de Comercio Exterior ante el Ministerio de Comercio Exterior y/o cualquier entidad del Estado que haga sus veces. En consecuencia, el Sr. MARLON TATIS PAREDES, podra suscribir en representacion de PROCAPS S.A. declaraciones, reportes y cualquier tipo de documentos relacionados con tramites o registros de Comercio Exterior ante el Ministerio de Comercio Exterior y/o cualquier entidad del Estado que haga sus veces.-----

C E R T I F I C A

Que segun documento privado del 10 de noviembre del 2004, inscrito en esta Camara de Comercio el 1 de diciembre del 2.004, bajo el No. 2.753 del libro respectivo consta que RUBEN MINSNSKI GONTOVNIK, C.C. 7.463.982 de Barranquilla, actuando como Presidente y Representante Legal de la sociedad PROCAPS S.A, confiere poder especial, amplio y suficiente a ANTONIO VARELA DIAZ, C.C.No.72.004.669 de Barranquilla, para que en nombre y representacion de la sociedad firme las declaraciones cambiarias a que este obligada PROCAPS S.A., a suscribir en el giro normal de sus negocios y operaciones socia-

***** C O N T I N U A *****



***** Pag. 6
C A M A R A D E C O M E R C I O
D E B A R R A N Q U I L L A
09*****

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.

PROCAPS S.A.-----

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m. Rojas

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(54) Title: OSMOTIC DEVICE CONTAINING VENLAFAXINE AND AN ANTI-PSYCHOTIC AGENT

(57) Abstract: The present invention provides an osmotic device containing controlled release venlafaxine in the core in combination with an anti-psychotic agent in a rapid release external coat. A wide range of anti-psychotic agents can be used in this device. Particular embodiments of the invention provide osmotic devices having predetermined release profiles. One embodiment of the osmotic device includes an external coat that has been spray-coated rather compression-coated onto the device. The device with spray-coated external core is smaller and easier to swallow than the similar device having a compression-coated external coat. The device is useful for the treatment of depression anxiety or psychosis related disorders.

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OSMOTIC DEVICE CONTAINING VENLAFAXINE AND AN ANTI-PSYCHOTIC AGENT

FIELD OF THE INVENTION

This invention pertains to an osmotic device containing venlafaxine. More particularly, it pertains to an osmotic device tablet that provides a controlled release of venlafaxine, and optionally an anti-psychotic agent, following a particularly advantageous
5 release profile.

BACKGROUND OF THE INVENTION

Clinical depression is a disorder characterized by low self-esteem, guilt, self-reproach, introversion, sadness, despair, sleeping disorders, eating disorders or discouragement. Depression generally causes a lower or decrease of a person's function.
10 Anxiety is a disorder characterized by responses to anticipation of unreal or imagined danger. It manifests itself as increased heart rate, altered respiration rate, sweating, trembling, weakness, or fatigue. Psychosis is a disorder characterized by gross impairment in reality perception as evidenced by delusions, hallucinations, markedly incoherent speech, or disorganized and agitated behavior without apparent awareness on the part of
15 the person of the incomprehensibility of his behavior.

Major depression and anxiety occur concomitantly in more patients than either one alone. When these disorders occur together, they are associated with more severe symptoms, increased impairment of function, a longer chronic course, poorer outcome, and a higher incidence of suicide.

20 Antidepressants, such as venlafaxine, have been tested for the treatment of depression and symptoms of anxiety. Anti-psychotic agents, such as risperidone, are used for the treatment of psychosis. On occasion, a person suffering from depression or anxiety and psychosis will be prescribed an antidepressant agent and an anti-psychotic agent.

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Rather than administration of two different dosages, it would be useful in the art to have available a single dosage containing both an antidepressant and an anti-psychotic.

Venlafaxine is commercially available in an extended release capsule dosage form from Wyeth Ayerst under the trademark EFFEXOR XR™. The capsule is available in
5 37.5, 75, and 150 mg strengths. The capsule is disclosed in U.S. Patent No. 4,535,186 and does not contain the venlafaxine in combination with an anti-psychotic agent. Moreover, the EFFEXOR XR™ formulation provides an incomplete release of venlafaxine.

Bymaster et al. (European Patent Application No. EP 0830864 A1) disclose a method, and compositions and dosage forms therefor, of treating psychoses with a
10 combination of a serotonin uptake inhibitor and an anti-psychotic agent. Bymaster et al. do not disclose an osmotic device containing such combination nor the beneficial effects of sequential administration of the two drugs, one rapid release and the other controlled release, from a single dosage form.

Controlled release capsule dosage forms and osmotic device dosage forms are
15 generally known by the skilled artisan to provide different release profiles. Effective therapy with antidepressants and anxiolytic agents is dependent upon a careful control of the blood plasma levels of these agents, and therefore, upon the release profiles of these agents from their respective dosage forms.

Osmotic devices and other tablet formulations are known for their ability to provide a
20 controlled release of a wide range of drugs. Such osmotic devices and other tablet formulations are disclosed in U.S. Patent No. 4,014,334 to Theeuwes et al., U.S. Patent No. 4,576,604 to Guittard et al., Argentina Patent No. 234,493, U.S. Patent No. 4,673,405 to Guittard et al., U.S. Patent No. 5,558,879 to Chen et al., U.S. Patent No. 4,810,502 to Ayer et al., U.S. Patent No. 4,801,461 to Hamel et al., U.S. Patent No. 5,681,584 to Savastano et al.,
25 US Patent No. 3,845,770, U.S. Patent No. 6,004,582 to Faour et al., and Argentina Patent No. 199,301, the entire disclosures of which are hereby incorporated by reference.

These references, however, do not disclose osmotic devices that provide the specific plasma profiles or release profiles for venlafaxine (VFX), and an optional anti-psychotic agent, that the present invention provides. Moreover, the prior art does not
30 disclose an osmotic device containing a combination of venlafaxine with an anti-psychotic

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agent, and generally wherein the venlafaxine and anti-psychotic agent are delivered according to specific release profiles that are advantageous over known formulations.

SUMMARY OF THE INVENTION

In one aspect, the present invention provides an osmotic device comprising:

5 a core comprising a therapeutically effective amount of venlafaxine and at least one osmotic agent or osmopolymer; and

a semipermeable membrane surrounding the core and having a passageway there through;

wherein the core provides a controlled release of VFX, and at least 80% of the
10 VFX is released within 13 hours after exposure of the osmotic device to an aqueous solution.

Another aspect of the present invention provides an osmotic device for the delivery of VFX and an anti-psychotic agent comprising:

15 a core comprising a therapeutically effective amount of venlafaxine and at least one osmotic agent or osmopolymer;

a semipermeable membrane surrounding the core and having a passageway there through; and

an external coat comprising a therapeutically effective amount of an anti-psychotic agent;

20 wherein the core provides a controlled release of VFX, and at least 80% of the VFX is released within 13 hours after exposure of the osmotic device to an aqueous solution, and the external coat provides a rapid release of the anti-psychotic agent, and at least 75% of the anti-psychotic agent is released within 1 hour after exposure of the osmotic device to an aqueous solution.

25 In some embodiments, the external coat is applied by spray coating or compression coating. By spray coating rather than compression coating the external coat, a thinner external coat, and therefore a smaller osmotic device, is formed.

Another aspect of the invention provides a method of treating depression, anxiety and/or psychosis in a mammal, the method comprising the step of administering an
30 osmotic device which provides a controlled release of VFX from its core and a rapid release of an anti-psychotic agent from an external coat, wherein at least 75% of the anti-

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psychotic agent is released within about 40 minutes, and at least about 60% of the VFX is released within about 12 hours after administration.

In other embodiments, the osmotic device provides: a) a VFX release profile similar to that shown in Figure 1; or b) a VFX plasma profile similar to that shown in
5 Figures 2 or 4. In still other embodiments, the release of VFX and/or the anti-psychotic agent has a delayed onset.

In even other embodiments, the anti-psychotic agent is selected from the group consisting of risperidone, olanzapine, clozapine, sertindole, ziprasidone, quetiapine, sulpiride, pimozide, clothiapine, molindone, loxapine, trifluoperazine, haloperidol,
10 flupenthixol, chlorpromazine, chlorprothixene, clopenthixol, droperidol, perphenazine, fluphenazine, lithium, mesoridazine, spiperone, promazine, prochlorperazine, thioridazine, thiothixene, triflupromazine, and raclopride.

In yet other embodiments, the following anti-psychotic agents are administered in the indicated doses: a) risperidone- 5 to 10 mg per day; b) olanzapine- 5 to 20 mg, 0.25-50
15 mg, 1-30 mg, or 1-25 mg per day; c) clozapine- 100 to 400 mg, 12.5-900 mg, or 150-450 mg per day; d) sertindole- 15 to 20 mg per day or 0.0001 to 1.0 mg/kg of body weight per day; e) ziprasidone- 80 to 160 mg, 5 to 500 mg or 50 to 100 mg per day; f) quetiapine- 150 to 600 mg or 1.0-40 mg/kg of body weight per day; g) sulpiride- 50 to 100 mg per day; h) pimozide- 2 to 4 mg per day; or i) clothiapine- 40 mg per day.

20 The venlafaxine, as either its free base or salt form, will be administered once daily in doses ranging from about 10 to 150 mg, 25 to 125 mg, 150 to 300 mg, or 10-500 mg.

The osmotic device generally delivers the anti-psychotic agent to the upper GI tract and the venlafaxine to the middle to lower GI tract.

Other features, advantages and embodiments of the invention will become apparent
25 to those skilled in the art by the following description, accompanying examples.

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BRIEF DESCRIPTION OF THE FIGURES

The following drawings are part of the present specification and are included to further demonstrate certain aspects of the invention. The invention may be better understood by reference to one or more of these drawings in combination with the detailed description of the specific embodiments presented herein.

FIG. 1 depicts an *in vitro* release profile for VFX from the exemplary formulation of Example 1.

FIG. 2 depicts an *in vivo* plasma profile for VFX from the exemplary formulation of Example 1.

FIG. 3 depicts an *in vivo* plasma profile for the commercial product EFFEXOR ER.

FIG. 4 depicts a comparative plot including the plasma profiles of FIGS. 2 and 3.

DETAILED DESCRIPTION OF THE INVENTION

Venlafaxine and anti-psychotic agents are available from a large number of commercial sources. The invention provides for the administration of venlafaxine alone or in combination with an anti-psychotic agent, wherein these compounds are in their free base, free acid, racemic, optically pure, diastereomeric and/or pharmaceutically acceptable salt forms.

As used herein, "pharmaceutically acceptable salts" refer to derivatives of the disclosed compounds wherein the therapeutic compound is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of the VFX or anti-psychotic agent. The pharmaceutically acceptable salts include the conventional non-toxic salts, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfonic, sulfamic, phosphoric, nitric and the like; and the salts prepared from organic acids such as amino acids, acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pantoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, and the like. Lists of suitable salts are found in *Remington's Pharmaceutical Sciences*, 17th ed., Mack Publishing Company, Easton, PA, 1985, p. 1418, the disclosure of which is hereby incorporated by reference.

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The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

FIG. 1 depicts various venlafaxine *in vitro* release profiles for the osmotic device tablets described in Example 1 (average of 6 runs). This formulation exhibits a 22-hour or greater controlled release of VFX. The VFX release profile of this exemplary formulation is generally described as follows:

10

Time (h)	Maximum Percent Released	Minimum Percent Released
1	9.0	5.6
3	24.1	22.8
5	46.6	41.0
7	62.7	55.9
9	72.9	66.6
11	79.0	73.9
13	83.4	78.6
15	86.6	81.8
19	90.1	86.3
23	≥92.9	89.0

The venlafaxine release profile can also be described as follows:

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Time (h)	Released (%)	STD (%)
1	7.2	1.3
3	23.6	0.5
5	43.3	2.1
7	59.0	2.3
9	69.7	2.1
11	77.0	1.8
13	81.8	1.7
15	84.7	1.7
19	88.1	1.4
23	≥90.8	1.5

FIG 2. Depicts an VFX *in vivo* plasma profile for the osmotic device tablets described in Example 1 (mean $\pm$ S.D., n= 12 runs). This exemplary device provides therapeutically effective levels of VFX between the period of about 1 to about 36 hours after administration. Therapeutic VFX plasma concentration levels range from about 2 to about 37 ng/ml, generally about 2 to about 22 ng/ml. The mean $C_{\max}$ is about 19 ng of VFX per ml of plasma at about 8-10 hours after administration. The *in vivo* plasma profile can be characterized as follows:

Time after Administration (h)	Mean VFX Plasma Concentration (ng/ml)	S.E.M.
0	0.0	0.0
0.5	0.3	0.2
1	0.4	0.2
2	3.2	0.8
4	13.9	2.6
6	17.5	2.5
8	18.7	2.7
10	18.8	2.9

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Time after Administration (h)	Mean VFX Plasma Concentration (ng/ml)	S.E.M.
12	16.7	2.5
14	15.8	2.7
16	11.8	2.0
20	8.6	1.7
24	6.6	1.1
28	5.7	1.5
32	3.4	0.7
36	2.2	0.5
48	1.7	0.5

SD denotes "standard deviation".

The osmotic device generally provides the above-described plasma profile after administration of a single daily dose, i.e. acute dosing. The artisan of ordinary skill will understand that chronic daily dosing of the osmotic device will generally result in a relatively flat plasma profile over a 24-hour period for venlafaxine and optionally the anti-psychotic agent, since a steady-state or equilibrium will be reached due to chronic administration.

FIG 3. depicts an VFX *in vivo* plasma profile for the EFFEXOR ER 75 mg product (mean $\pm$ S.D., n=12). The mean C_{max} for the commercial product is about 23 ng of VFX per ml of plasma at about 8-10 hours after administration. FIG. 5 depicts comparative data for the *in vivo* VFX of the formulations of the invention and of the commercial product. The data shows absolute differences in the C_{max} and T_{max} values achieved.

Calculated PK parameters			Bioequivalence evaluation		
Parameter	Example 1 (75 mg)	REF (EFFEXOR [®] ER 75 mg)	Geometric mean Relative bioavailability %	90% Confidence Interval	Bioequivalence Limits
ABC_{∞} (ng.h/ml)	388.8 $\pm$ 64.4	398.5 $\pm$ 71.6	99.4	92.2 - 102.9	80 - 120
C_{max} (ng/ml)	20.4 $\pm$ 2.8	23.4 $\pm$ 3.3	87.8	81.9 - 92.9	80 - 120
C_{max}/ABC_{∞}	0.057 $\pm$ 0.004	0.064 $\pm$ 0.005	88.5	82.8 - 93.2	80 - 120

Calculated PK parameters			Bioequivalence evaluation		
Parameter	Example 1 (75 mg)	REF (EFFEXOR [®] ER 75 mg)	Geometric mean Relative bioavailability %	90% Confidence Interval	Bioequivalence Limits
t_{max} (h)	9.0±2.0	6.0±2.5	-----	-----	-----
K_e (h ⁻¹)	0.077±0.007	0.079±0.010	-----	-----	-----

The release profile of the osmotic device of the invention is preferred as it provides a lower C_{max} and longer T_{max} while at the same time maintaining therapeutically effective levels thereof over an extended period of time.

- 5 Depending upon the particular combination of ingredients used to prepare the osmotic device, it will generally provide an expected overall venlafaxine release profile resembling a pseudo-first order, first-order, pseudo-second order, second order, pseudo-third order or third order release profile.

- 10 All of the tablet formulations of the invention will provide therapeutically effective levels of venlafaxine and an anti-psychotic agent for at least a predetermined period of time. The tablets of the invention will generally provide therapeutically effective amounts of venlafaxine for a total time period of not less than 18 hours and not more than 30 hours, generally not less than 20 hours and not more than 24 hours, or not less than 22 hours.

- 15 The external coating can be an immediately dissolving coating that dissolves in the buccal cavity or a rapidly dissolving coating that dissolved in the stomach, jejunum or duodenum. The controlled release core generally begins to release venlafaxine within about 2 hours after administration.

- 20 The rapid release coating will release all of its anti-psychotic agent within three hours after administration and preferably at least 75% of its anti-psychotic agent within about 40 minutes after administration. While the anti-psychotic agent is released over a short period of time, the therapeutic benefit that it provides will last at least 12 hours and generally up to about 24 hours. The actual time period will vary according to the anti-psychotic agent used and, in particular, its half-life in a patient.

- 25 Those of ordinary skill in the art will appreciate that the particular amounts of venlafaxine and anti-psychotic agent used in the osmotic device will vary according to, among other things, the desired pharmacokinetic behavior in a mammal.

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When a rapidly dissolving coat is used in the tablet formulations of the invention, the coat will generally comprise an inert and non-toxic material that is at least partially, and generally substantially completely, soluble or erodible in an environment of use. The rapidly dissolving coat will be soluble in the buccal cavity and/or upper GI tract, such as the stomach, duodenum, jejunum or upper small intestines. Exemplary materials are disclosed in U.S. Patents No. 4,576,604 and 4,673,405, and the text Pharmaceutical Dosage Forms: Tablets Volume I, Second Edition. A. Lieberman. ed. 1989, Marcel Dekker, Inc. the relevant disclosures of which are hereby incorporated by reference. In embodiments, the rapidly dissolving coat will be soluble in saliva, gastric juices, or acidic fluids.

The long acting controlled release tablet formulations that provide a delayed and sustained release of venlafaxine may include an enteric coat that is soluble or erodible in intestinal juices, substantially pH neutral or basic fluids but for the most part insoluble in gastric juices or acidic fluids. A wide variety of other polymeric materials are known to possess these various solubility properties. Such other polymeric materials include, by way of example and without limitation, cellulose acetate phthalate (CAP), cellulose acetate trimellitate (CAT), poly(vinyl acetate) phthalate (PVAP), hydroxypropyl methylcellulose phthalate (HP), poly(methacrylate ethylacrylate) (1:1) copolymer (MA-EA), poly(methacrylate methylmethacrylate) (1:1) copolymer (MA-MMA), poly(methacrylate methylmethacrylate) (1:2) copolymer, Eudragit L-30-D™ (MA-EA, 1:1), Eudragit™ L-100-55™ (MA-EA, 1:1), hydroxypropyl methylcellulose acetate succinate (HPMCAS), Coateric™ (PVAP), Aquateric™ (CAP), AQUACOAT™ (HPMCAS) and combinations thereof. The enteric coat can also comprise dissolution aids, stability modifiers, and bioabsorption enhancers.

When the enteric coat is intended to be dissolved, eroded or become detached from the core in the colon, materials such as hydroxypropylcellulose, microcrystalline cellulose (MCC, Avicel™ from FMC Corp.), poly (ethylene - vinyl acetate) (60:40) copolymer (EVAC from Aldrich Chemical Co.), 2-hydroxyethylmethacrylate (HEMA), MMA, terpolymers of HEMA: MMA:MA synthesized in the presence of N,N'-bis(methacryloyloxyethyloxycarbonylamino) - azobenzene, azopolymers, enteric coated timed release system (Time Clock® from Pharmaceutical Profiles, Ltd., UK) and calcium pectinate can be used.

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A polymeric material for use in the enteric coat involves enteric materials that resist the action of gastric fluid avoiding permeation through the semipermeable wall while one or more of the materials in the core of the tablet are solubilized in the intestinal tract thereby allowing delivery of the venlafaxine in the core by osmotic pumping in an osmotic device to begin. A material that easily adapts to this kind of requirement is a poly(vinylpyrrolidone)-vinyl acetate copolymer, such as the material supplied by BASF under its Kollidon VA64 trademark, mixed with magnesium stearate and other similar excipients. The enteric coat can also comprise povidone, which is supplied by BASF under its Kollidon K 30 trademark, and hydroxypropyl methylcellulose, which is supplied by Dow under its Methocel E-15 trademark. The materials can be prepared in solutions of having different concentrations of polymer according to the desired solution viscosity. For example, a 10% P/V aqueous solution of Kollidon K 30 has a viscosity of about 5.5-8.5 cps at 20 °C, and a 2% P/V aqueous solution of Methocel E-15 has a viscosity of about 13-18 cps at 20 °C.

The enteric coat can comprise one or more materials that do not dissolve, disintegrate, or change their structural integrity in the stomach and during the period of time that the tablet resides in the stomach. Representative materials that keep their integrity in the stomach can comprise a member selected from the group consisting of (a) keratin, keratin sandarac-tolu, salol (phenyl salicylate), salol beta-naphthylbenzoate and acetotannin, salol with balsam of Peru, salol with tolu, salol with gum mastic, salol and stearic acid, and salol and shellac; (b) a member selected from the group consisting of formalized protein, formalized gelatin, and formalized cross-linked gelatin and exchange resins; (c) a member selected from the group consisting of myristic acid-hydrogenated castor oil-cholesterol, stearic acid-mutton tallow, stearic acid-balsam of tolu, and stearic acid-castor oil; (d) a member selected from the group consisting of shellac, ammoniated shellac, ammoniated shellac-salol, shellac-wool fat, shellac-acetyl alcohol, shellac-stearic acid-balsam of tolu, and shellac n-butyl stearate; (e) a member selected from the group consisting of abietic acid, methyl abietate, benzoin, balsam of tolu, sandarac, mastic with tolu, and mastic with tolu, and mastic with acetyl alcohol; (f) acrylic resins represented by anionic polymers synthesized from methacrylate acid and methacrylic acid methyl ester, copolymeric acrylic resins of methacrylic and methacrylic acid and methacrylic acid alkyl

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esters, copolymers of alkacrylic acid and alkacrylic acid alkyl esters, acrylic resins such as dimethylaminoethylmethacrylate-butylmethacrylate-methylmethacrylate copolymer of 150,000 molecular weight, methacrylic acid-methylmethacrylate 50:50 copolymer of 135,000 molecular weight, methacrylic acid-methylmethacrylate-30:70-copolymer of 135,000 mol. wt., methacrylic acid-dimethylaminoethyl-methacrylate-ethylacrylate of 750,000 mol. wt., methacrylic acid-methylmethacrylate-ethylacrylate of 1,000,000 mol. wt., and ethylacrylate-methylmethacrylate-ethylacrylate of 550,000 mol. wt; and, (g) an enteric composition comprising a member selected from the group consisting of cellulose acetyl phthalate, cellulose diacetyl phthalate, cellulose triacetyl phthalate, cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, sodium cellulose acetate phthalate, cellulose ester phthalate, cellulose ether phthalate, methylcellulose phthalate, cellulose ester-ether phthalate, hydroxypropyl cellulose phthalate, alkali salts of cellulose acetate phthalate, alkaline earth salts of cellulose acetate phthalate, calcium salt of cellulose acetate phthalate, ammonium salt of hydroxypropyl methylcellulose phthalate, cellulose acetate hexahydrophthalate, hydroxypropyl methylcellulose hexahydrophthalate, polyvinyl acetate phthalate diethyl phthalate, dibutyl phthalate, dialkyl phthalate wherein the alkyl comprises from 1 to 7 straight and branched alkyl groups, aryl phthalates, and other materials known to one of ordinary skill in the art.

The semipermeable membrane of the osmotic device is formed of a material that is substantially permeable to the passage of fluid from the environment of use to the core and substantially impermeable to the passage of active agent from the core. Many common materials known by those of ordinary skill in the art are suitable for this purpose. Exemplary materials are cellulose esters, cellulose ethers and cellulose esters-ethers. However, it has been found that a semipermeable membrane consisting essentially of cellulose acetate (CA) and poly(ethylene glycol) (PEG), in particular PEG 400, are when used in combination with the other materials required in the present osmotic device. This particular combination of CA and PEG provides a semipermeable membrane that gives the osmotic device a well controlled release profile for the active agent in the core and that retains its chemical and physical integrity in the environment of use. The ratio of CA:PEG generally ranges from about 50-99% by weight of CA: about 50-1% by weight of PEG, and generally about 95% by weight of CA: about 5% by weight of PEG. The ratio can be

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varied to alter permeability and ultimately the release profile of the osmotic device. Other materials can include a selected member of the group of cellulose acylates such as cellulose acetate, cellulose diacetate, cellulose triacetate and combinations thereof. Many suitable polymers, include those disclosed in Argentine Patent No. 199,301 and other references cited herein, the disclosures of which are hereby incorporated by reference.

The core of the osmotic device tablet of the present invention will comprise venlafaxine, at least one pharmaceutically acceptable excipient and optionally one or more other materials. Generally, the tablet formulations will comprise about 0.1-99.9% by weight of venlafaxine in the uncoated tablet core. ranges will vary according to the anti-psychotic agent used and the intended use of the osmotic device.

When the controlled release tablet is an osmotic device, osmotically effective solutes, osmotic agents or osmagents are added. These osmagents can aid in either the suspension or dissolution of the VFX in the core. Exemplary osmagents include organic and inorganic compounds such as salts, acids, bases, chelating agents, sodium chloride, lithium chloride, magnesium chloride, magnesium sulfate, lithium sulfate, potassium chloride, sodium sulfite, calcium bicarbonate, sodium sulfate, calcium sulfate, calcium lactate, d-mannitol, urea, tartaric acid, raffinose, sucrose, alpha-d-lactose monohydrate, glucose, combinations thereof and other similar or equivalent materials which are widely known in the art. Osmagents can also be incorporated to the core of the osmotic device to control the release of VFX therefrom.

The tablets of the invention can also comprise an acidifying agent, alkalizing agent, adsorbent, antioxidant, buffering agent, colorant, flavorant, sweetening agent, tablet antiadherent, tablet binder, tablet and capsule diluent, tablet direct compression excipient, tablet disintegrant, tablet glidant, tablet lubricant, tablet or capsule opaquant and/or tablet polishing agents.

As used herein, the term "adsorbent" is intended to mean an agent capable of holding other molecules onto its surface by physical or chemical (chemisorption) means. Such compounds include, by way of example and without limitation, powdered and activated charcoal and other materials known to one of ordinary skill in the art.

As used herein, the term "antioxidant" is intended to mean an agent that inhibits oxidation and thus is used to prevent the deterioration of preparations by the oxidative

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process. Such compounds include, by way of example and without limitation, ascorbic acid, ascorbyl palmitate, butylated hydroxyanisole, butylated hydroxytoluene, hypophosphorous acid, monothioglycerol, propyl gallate, sodium ascorbate, sodium bisulfite, sodium formaldehyde sulfoxylate and sodium metabisulfite and other materials known to one of
5 ordinary skill in the art.

As used herein, the term "alkalizing agent" is intended to mean a compound used to provide alkaline medium for product stability. Such compounds include, by way of example and without limitation, ammonia solution, ammonium carbonate, diethanolamine, monoethanolamine, potassium hydroxide, sodium borate, sodium carbonate, sodium
10 bicarbonate, sodium hydroxide, triethanolamine, and triethylamine and others known to those of ordinary skill in the art.

As used herein, the term "acidifying agent" is intended to mean a compound used to provide an acidic medium for product stability. Such compounds include, by way of example and without limitation, acetic acid, amino acid, citric acid, fumaric acid and other
15 alpha hydroxy acids, such as hydrochloric acid, ascorbic acid, and nitric acid and others known to those of ordinary skill in the art.

As used herein, the term "buffering agent" is intended to mean a compound used to resist change in pH upon dilution or addition of acid or alkali. Such compounds include, by way of example and without limitation, potassium metaphosphate, potassium phosphate,
20 monobasic sodium acetate and sodium citrate anhydrous and dihydrate and other materials known to one of ordinary skill in the art.

As used herein, the term "sweetening agent" is intended to mean a compound used to impart sweetness to a preparation. Such compounds include, by way of example and without limitation, aspartame, dextrose, glycerin, mannitol, saccharin sodium, sorbitol and sucrose
25 and other materials known to one of ordinary skill in the art.

As used herein, the term "tablet antiadherent" is intended to mean an agent which prevent the sticking of tablet formulation ingredients to punches and dies in a tableting machine during production. Such compounds include, by way of example and without limitation, magnesium stearate, talc, calcium stearate, glyceryl behenate, PEG, hydrogenated
30 vegetable oil, mineral oil, stearic acid and other materials known to one of ordinary skill in the art.

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As used herein, the term "tablet binder" is intended to mean a substance used to cause adhesion of powder particles in table granulations. Such compounds include, by way of example and without limitation, acacia, alginic acid, carboxymethylcellulose sodium, poly(vinylpyrrolidone), compressible sugar (e.g., NuTab), ethylcellulose, gelatin, liquid
5 glucose, methylcellulose, povidone and pregelatinized starch and other materials known to one of ordinary skill in the art.

When needed, binders may also be included in the tablets. Exemplary binders include acacia, tragacanth, gelatin, starch, cellulose materials such as methyl cellulose and sodium carboxy methyl cellulose, alginic acids and salts thereof, polyethylene glycol, guar
10 gum, polysaccharide, bentonites, sugars, invert sugars, poloxamers (PLURONIC F68, PLURONIC F127), collagen, albumin, gelatin, cellulotics in nonaqueous solvents, combinations thereof and the like. Other binders include, for example, polypropylene glycol, polyoxyethylene-polypropylene copolymer, polyethylene ester, polyethylene sorbitan ester, polyethylene oxide, combinations thereof and other materials known to one of ordinary skill
15 in the art.

As used herein, the term "tablet and capsule diluent" or "filler" is intended to mean inert substances used as fillers to create the desired bulk, flow properties, and compression characteristics in the preparation of tablets and capsules. Such compounds include, by way of example and without limitation, dibasic calcium phosphate, kaolin, lactose, sucrose,
20 mannitol, microcrystalline cellulose, powdered cellulose, precipitated calcium carbonate, sorbitol, and starch and other materials known to one of ordinary skill in the art.

As used herein, the term "tablet direct compression excipient" is intended to mean a compound used in direct compression tablet formulations. Such compounds include, by way of example and without limitation, dibasic calcium phosphate (e.g., Datab) and other
25 materials known to one of ordinary skill in the art.

As used herein, the term "tablet glidant" is intended to mean agents used in tablet and capsule formulations to reduce friction during tablet compression. Such compounds include, by way of example and without limitation, colloidal silica, cornstarch, talc, calcium silicate, magnesium silicate, colloidal silicon, silicon hydrogel and other materials known to one of
30 ordinary skill in the art.

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As used herein, the term "tablet lubricant" is intended to mean substances used in tablet formulations to reduce friction during tablet compression. Such compounds include, by way of example and without limitation, calcium stearate, magnesium stearate, mineral oil, stearic acid, and zinc stearate and other materials known to one of ordinary skill in the art.

5 As used herein, the term "tablet/capsule opaquant" is intended to mean a compound used to render a capsule or a tablet coating opaque. May be used alone or in combination with a colorant. Such compounds include, by way of example and without limitation, titanium dioxide and other materials known to one of ordinary skill in the art.

As used herein, the term "tablet polishing agent" is intended to mean a compound
10 used to impart an attractive sheen to coated tablets. Such compounds include, by way of example and without limitation, carnauba wax, and white wax and other materials known to one of ordinary skill in the art.

As used herein, the term "tablet disintegrant" is intended to mean a compound used in solid dosage forms to promote the disruption of the solid mass into smaller particles which
15 are more readily dispersed or dissolved. Exemplary disintegrants include, by way of example and without limitation, starches such as corn starch, potato starch, pre-gelatinized and modified starches thereof, sweeteners, clays, such as bentonite, microcrystalline cellulose(e.g., Avicel), carboxymethylcellulose calcium, cellulose polyacrilin potassium (e.g., Amberlite), alginates, sodium starch glycolate, gums such as agar, guar, locust bean, karaya,
20 pectin, tragacanth and other materials known to one of ordinary skill in the art.

As used herein, the term "colorant" is intended to mean a compound used to impart color to solid (e.g., tablets) pharmaceutical preparations. Such compounds include, by way of example and without limitation, FD&C Red No. 3, FD&C Red No. 20, FD&C Yellow No. 6, FD&C Blue No. 2, D&C Green No. 5, D&C Orange No. 5, D&C Red No. 8, caramel,
25 and ferric oxide, red, other F.D. & C. dyes and natural coloring agents such as grape skin extract, beet red powder, beta-carotene, annato, carmine, turmeric, paprika, and other materials known to one of ordinary skill in the art. The amount of coloring agent used will vary as desired.

As used herein, the term "flavorant" is intended to mean a compound used to impart a
30 pleasant flavor and often odor to a pharmaceutical preparation. Exemplary flavoring agents or flavorants include synthetic flavor oils and flavoring aromatics and/or natural oils, extracts

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from plants, leaves, flowers, fruits and so forth and combinations thereof. These may also include cinnamon oil, oil of wintergreen, peppermint oils, clove oil, bay oil, anise oil, eucalyptus, thyme oil, cedar leave oil, oil of nutmeg, oil of sage, oil of bitter almonds and cassia oil. Other useful flavors include vanilla, citrus oil, including lemon, orange, grape, 5 lime and grapefruit, and fruit essences, including apple, pear, peach, strawberry, raspberry, cherry, plum, pineapple, apricot and so forth. Flavors which have been found to be particularly useful include commercially available orange, grape, cherry and bubble gum flavors and mixtures thereof. The amount of flavoring may depend on a number of factors, including the organoleptic effect desired. Flavors will be present in any amount as desired by 10 those of ordinary skill in the art. Particular flavors are the grape and cherry flavors and citrus flavors such as orange.

The present tablets can also employ one or more commonly known surface active agents or cosolvents that improve wetting or disintegration of the tablet core or layers.

Plasticizers can also be included in the tablets to modify the properties and 15 characteristics of the polymers used in the coats or core of the tablets. As used herein, the term "plasticizer" includes all compounds capable of plasticizing or softening a polymer or binder used in invention. The plasticizer should be able to lower the melting temperature or glass transition temperature (softening point temperature) of the polymer or binder. Plasticizers, such as low molecular weight PEG, generally broaden the average molecular 20 weight of a polymer in which they are included thereby lowering its glass transition temperature or softening point. Plasticizers also generally reduce the viscosity of a polymer. It is possible the plasticizer will impart some particularly advantageous physical properties to the osmotic device of the invention.

Plasticizers useful in the invention can include, by way of example and without 25 limitation, low molecular weight polymers, oligomers, copolymers, oils, small organic molecules, low molecular weight polyols having aliphatic hydroxyls, ester-type plasticizers, glycol ethers, poly(propylene glycol), multi-block polymers, single block polymers, low molecular weight poly(ethylene glycol), citrate ester-type plasticizers, triacetin, propylene glycol and glycerin. Such plasticizers can also include ethylene glycol, 1,2-butylene glycol, 30 2,3-butylene glycol, styrene glycol, diethylene glycol, triethylene glycol, tetraethylene glycol and other poly(ethylene glycol) compounds, monopropylene glycol monoisopropyl ether,

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propylene glycol monoethyl ether, ethylene glycol monoethyl ether, diethylene glycol monoethyl ether, sorbitol lactate, ethyl lactate, butyl lactate, ethyl glycolate, dibutylsebacate, acetyltributylcitrate, triethyl citrate, acetyl triethyl citrate, tributyl citrate and allyl glycolate. All such plasticizers are commercially available from sources such as Aldrich or Sigma Chemical Co. It is also contemplated and within the scope of the invention, that a combination of plasticizers may be used in the present formulation. The PEG based plasticizers are available commercially or can be made by a variety of methods, such as disclosed in *Poly(ethylene glycol) Chemistry: Biotechnical and Biomedical Applications* (J.M. Harris, Ed.; Plenum Press, NY) the disclosure of which is hereby incorporated by reference.

The tablets of the invention can also include oils, for example, fixed oils, such as peanut oil, sesame oil, cottonseed oil, corn oil and olive oil; fatty acids, such as oleic acid, stearic acid and isotearic acid; and fatty acid esters, such as ethyl oleate, isopropyl myristate, fatty acid glyceridees and acetylated fatty acid glycerides. It can also be mixed with alcohols, such as ethanol, isopropanol, hexadecyl alcohol, glycerol and propylene glycol; with glycerol ketals, such as 2,2-dimethyl-1,3-dioxolane-4-methanol; with ethers, such as poly(ethyleneglycol) 450, with petroleum hydrocarbons, such as mineral oil and petrolatum; with water, or with mixtures thereof; with or without the addition of a pharmaceutically suitable surfactant, suspending agent or emulsifying agent.

Soaps and synthetic detergents may be employed as surfactants and as vehicles for detergent compositions. Suitable soaps include fatty acid alkali metal, ammonium, and triethanolamine salts. Suitable detergents include cationic detergents, for example, dimethyl dialkyl ammonium halides, alkyl pyridinium halides, and alkylamine acetates; anionic detergents, for example, alkyl, aryl and olefin sulfonates, alkyl, olefin, ether and monoglyceride sulfates, and sulfosuccinates; nonionic detergents, for example, fatty amine oxides, fatty acid alkanolamides, and poly(oxyethylene)-*block*-poly(oxypropylene) copolymers; and amphoteric detergents, for example, alkyl β -aminopropionates and 2-alkylimidazoline quaternary ammonium salts; and mixtures thereof.

Various other components, not otherwise listed above, can be added to the present formulation for optimization of a desired active agent release profile including, by way of example and without limitation, glycerylmonostearate, nylon, cellulose acetate butyrate, d, l-

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poly(lactic acid), 1,6 - hexanediamine, diethylenetriamine, starches, derivatized starches, acetylated monoglycerides, gelatin coacervates, poly (styrene - maleic acid) copolymer, glycowax, castor wax, stearyl alcohol, glycerol palmitostearate, poly(ethylene), poly(vinyl acetate), poly(vinyl chloride), 1,3 - butylene-glycoldimethacrylate, ethyleneglycol-dimethacrylate and methacrylate hydrogels.

It should be understood, that compounds used in the art of pharmaceutical formulation generally serve a variety of functions or purposes. Thus, if a compound named herein is mentioned only once or is used to define more than one term herein, its purpose or function should not be construed as being limited solely to that named purpose(s) or function(s).

By the term "effective amount", it is understood that, with respect to, for example, pharmaceuticals, a therapeutically effective amount is contemplated. A therapeutically effective amount is the amount or quantity of venlafaxine which is sufficient to elicit the required or desired therapeutic response, or in other words, the amount which is sufficient to elicit an appreciable biological response when administered to a patient.

The tablets (osmotic devices) of the invention can assume any shape or form known in the art of pharmaceutical sciences. The device of the invention can be a pill, sphere, tablet, bar, plate, paraboloid of revolution, ellipsoid of revolution or the like. The tablets can also include surface markings, cuttings, grooves, letters and/or numerals for the purposes of decoration, identification and/or other purposes.

The tablets (osmotic devices) of the invention can be prepared according to the methods disclosed herein or those well known in the art, more specifically according to the methods disclosed in the disclosure incorporated herein by reference. For example, according to one manufacturing technique, venlafaxine and excipients that comprise the core are mixed in solid, semisolid or gelatinous form, then moistened and sieved through a specified screen to obtain uncoated cores. The uncoated cores are then dried in a dryer and compressed, for example, by punching. The compressed and uncoated cores are then covered with a semipermeable membrane. Subsequently, the semipermeable membrane surrounding the core should be perforated with, for example, laser equipment. Finally, an external coat containing the anti-psychotic agent is applied to the semipermeable membrane.

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The external coat can be applied as a compression coating, but it is generally applied as a sprayed coating. The sprayed coating is thinner and lighter than the compression coating, and an osmotic device including the sprayed on external coating is, therefore, smaller than a similar osmotic device having a compression coat. A smaller size osmotic device generally results in increased patient compliance in taking the osmotic device and is therefore advantageous.

The tablets (osmotic devices) of the invention can be coated with a finish coat as is commonly done in the art to provide the desired shine, color, taste or other aesthetic characteristics. Materials suitable for preparing the finish coat are well known in the art and found in the disclosures of many of the references cited and incorporated by reference herein.

The osmotic device of the invention comprises at least one passageway (pore, hole, or aperture) which communicates the exterior of the semipermeable wall with the core of the device. The passageway can be formed according to any of the known methods of forming passageways in a semipermeable membrane. Such methods include, for example, 1) drilling a hole through the semipermeable membrane with a bit or laser; 2) including a water soluble material within the composition that forms the semipermeable membrane such that a pore forms when the osmotic device is in an aqueous environment of use; 3) punching a hole through the semipermeable membrane; or 4) employing a tablet punch having a pin to punch a hole through the semipermeable lamina. The passageway can pass through the semipermeable wall and one or more of any other lamina coated onto the semipermeable membrane or between the semipermeable membrane and the core. The passageway(s) can be shaped as desired. In some embodiments, the passageway is laser drilled and is shaped as an oval, ellipse, slot, slit, cross or circle.

Methods of forming passageways in semipermeable membranes of osmotic devices are disclosed in U.S. Patents No. 4,088,864 to Theeuwes et al., No. 4,016,880 to Theeuwes et al., No. 3,916,899 to Theeuwes et al., No. 4,285,987 to Ayer et al., No. 4,783,337 to Wong et al., No. 5,558,879 to Chen et al., No. 4,801,461 to Hamel et al., and No. 3,845,770 to Theeuwes et al., the disclosures of which are hereby incorporated by reference.

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The preformed passageway, e.g., one made by mechanical means, is formed after the semipermeable membrane is applied to the core. It can be formed either before or after the inert water soluble coat and/or drug-containing external coat is applied to the semipermeable membrane.

5 The advantages of the present system over known systems for administering venlafaxine in combination with an anti-psychotic agent is improved therapeutic benefit, simplified manufacturing, and increased patient compliance. Moreover, the present formulation will provide an enhanced therapeutic effect when compared to the administration of venlafaxine alone.

10 By administration of the venlafaxine in a controlled release fashion and the anti-psychotic agent in a rapid release fashion, the osmotic device unexpectedly provides an improved pharmacological profile including reduced side effects, lower drug requirement and/or enhanced therapeutic benefit as compared to other known methods or dosage forms.

15 The osmotic device of the invention is useful for treating a variety of psychological disorders. The osmotic device can be used to treat psychotic conditions and mild anxiety with the atypical anti-psychotics without the concomitant weight gain typically observed with such treatment, conferring a marked and unexpected benefit on the patient. The present invention furthermore provides a potentiation of the increase in the concentration
20 of norepinephrine observed as an effect of administration of a first component compound, by administration of a second component compound.

The present invention is particularly suited for use in the treatment of bipolar disorders, mania (mixed state), schizoaffective disorders characterized by the occurrence of a depressive episode during the period of illness, and depression with psychotic
25 features. Such disorders may often be resistant to treatment with an anti-psychotic alone.

The present invention is also useful for the treatment of premenstrual syndrome (PMS) and anorexia nervosa. Furthermore, the present invention is useful for the treatment of the aggression/violence which may be associated with certain disorders. These disorders include, but are not limited to, mania, schizophrenia, schizoaffective disorders, substance
30 abuse, head injury, and mental retardation.

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Psychotic conditions to be treated by the present osmotic device include, for example, schizophrenia, schizophreniform diseases, acute mania, schizoaffective disorders, and depression with psychotic features. The titles given these conditions represent multiple disease states. The following list illustrates a number of these disease states, many of which are classified in the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, published by the American Psychiatric Association (DSM). The DSM code numbers for these disease states are supplied below, when available, for the convenience of the reader: Paranoid Type Schizophrenia 295.30; Disorganized Type Schizophrenia 295.10; Catatonic Type Schizophrenia 295.20; Undifferentiated Type Schizophrenia 295.90; Residual Type Schizophrenia 295.60; Schizophreniform Disorder 295.40; Schizoaffective Disorder 295.70; Schizoaffective Disorder of the Depressive Type; and Major Depressive Disorder with Psychotic Features 296.24, 296.34.

Psychoses are often associated with other diseases and conditions, or caused by such other conditions. For example, they are associated with neurological conditions, endocrine conditions, metabolic conditions, fluid or electrolyte imbalances, hepatic or renal diseases, and autoimmune disorders with central nervous system involvement. Psychoses may also be associated with use or abuse of certain substances. These substances include, but are not limited to cocaine, methylphenidate, dexamethasone, amphetamine and related substances, cannabis, hallucinogens, inhalants, opioids, phencyclidine, sedatives, hypnotics and anxiolytics. Psychotic disorders may also occur in association with withdrawal from certain substances. These substances include, but are not limited to, sedatives, hypnotics and anxiolytics. The embodiments of the present invention are useful for treatment of psychotic conditions associated with any of these conditions.

The following examples should not be considered exhaustive, but merely illustrative of only a few of the many embodiments contemplated by the present invention. The methods described herein can be followed to prepare osmotic devices according to the invention.

EXAMPLE 1

A scale batch of Venlafaxine HCl 75 mg was prepared by mixing 84.86 g of Venlafaxine HCl, 238.83 g of Mannitol and 25.0 g of Povidone. The mixture was wet with a blend of 120.00 ml of alcohol 96°, 22.31 g of Polyethylene Glycol 6000 and 1.50 g of

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Polyethylene Glycol 400. The blend was granulated and dried at 40 – 50°C for 3 hours; then, it was screened and mixed with 3.00 g of Colloidal Silicon Dioxide. The blend was mixed to homogeneity and 4.50 g of Magnesium Stearate was added as lubricant. The final blend was tabletted using biconcaves, 9.25-mm diameter punches. Cores weight: 380.0 mg. Hardness from 7 to 12 kp.

A first composition to cover the cores was prepared as follows: 7.53 g of Copolyvidone, 10.50 g of hydroxypropyl methylcellulose 2910, 3.00 g of Polyethylene Glycol 6000 and 3.97 g of Titanium Dioxide in Isopropyl Alcohol. This polymer mixture was sprayed onto the tablets in a conventional pan coater to obtain film-coated tablets which membrane coating weighed 25 mg approximately.

A second composition to cover the film-coated tablets was prepared as follows: 27.93 g of Cellulose Acetate and 1.47 g of Polyethylene Glycol 400 in a mixture of 495.0 ml of Methylene Chloride and 125.0 ml of Methyl Alcohol. This polymer mixture was sprayed onto the tablets in a conventional pan coater to obtain film-coated tablets which membrane coating weighed 29.4 mg approximately. A 0.50-mm hole was drilled through the coating in one face of the tablet.

The final coating was prepared by mixing 9.45 g of hydroxypropyl methylcellulose 2910, 6.78 g of Copolyvidone, 2.70 g of Polyethylene Glycol 6000, 3.20 g of Titanium Dioxide, 90.00 mg of Aluminum Lake Quinoline Yellow and 5.40 mg of Aluminum Lake Sunset Yellow in a mixture of Methylene Chloride-Alcohol 96° 70:30 v/v (volume/volume). This polymer mixture was sprayed onto the tablets in a conventional pan coater to obtain film-coated tablets which membrane coating weighed 15 mg approximately.

Tablets made according to the above procedure will generally have the following composition.

INGREDIENT	37.5 mg	75 mg	150 mg
<i>CORE</i>			
Venlafaxine Hydrochloride	42.430 mg	84.860 mg	169.720 mg
Mannitol	119.415 mg	238.830 mg	477.660 mg
Povidone	12.500 mg	25.00 mg	50.000 mg

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Polyethylene Glycol 400	0.750 mg	1.500 mg	3.000 mg
Colloidal Silicon Dioxide	1.500 mg	3.000 mg	6.000 mg
Polyethylene Glycol 6000	11.155 mg	22.310 mg	44.620 mg
Magnesium Stearate	2.250 mg	4.500 mg	9.000 mg

COATING A

Copolyvidone	5.420 mg	7.530 mg	11.930 mg
Hydroxypropyl methylcellulose 2910	7.560 mg	10.500 mg	16.630 mg
Polyethylene Glycol 6000	2.160 mg	3.000 mg	4.750 mg
Titanium Dioxide	2.860 mg	3.970 mg	6.290 mg

COATING B

Cellulose Acetate	23.040 mg	27.930 mg	60.440 mg
Polyethylene Glycol 400	1.210 mg	1.470 mg	4.130 mg

COATING C

Hydroxypropyl methylcellulose 2910	3.150 mg	6.300 mg	10.080 mg
Copolyvidone	2.260 mg	4.520 mg	7.230 mg
Polyethylene Glycol 6000	0.900 mg	1.800 mg	2.880 mg
Titanium Dioxide	1.158 mg	2.136 mg	3.709 mg
Aluminum Lake Quinoline Yellow	0.030 mg	0.060 mg	0.095 mg
Aluminum Lake Sunset Yellow	0.0018 mg	0.0036 mg	0.0060 mg

EXAMPLE 2

A large scale batch of venlafaxine and risperidone containing tablets was prepared by mixing 84.86 g of Venlafaxine HCl, 238.83 g of Mannitol and 25.0 g of Povidone. The mixture was wet with a blend of 120.00 ml of alcohol 96°, 22.31 g of Polyethylene Glycol 6000 and 1.50 g of Polyethylene Glycol 400. The blend was granulated and dried at 40 – 50°C for 3 hours; then, it was screened and mixed with 3.00 g of Colloidal Silicon Dioxide. The blend was mixed to homogenize and 4.50 g of Magnesium Stearate was added as lubricant. The final blend was tabletted using biconcaves, 9.25-mm diameter punches. Cores weight: 380.0 mg. Hardness from 7 to 12 kp.

A first composition to cover the cores was prepared as follows: 7.53 g of Copolyvidone, 10.50 g of hydroxypropyl methylcellulose 2910, 3.00 g of Polyethylene Glycol 6000 and 3.97 g of Titanium Dioxide in Isopropyl Alcohol. This polymer mixture was sprayed onto the tablets in a conventional pan coater to obtain film-coated tablets which membrane coating weighed 25 mg approximately.

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A second composition to cover the film-coated tablets was prepared as follows: 27.93 g of Cellulose Acetate and 1.47 g of Polyethylene Glycol 400 in a mixture of 495 ml of Methylene Chloride and 125 ml of Methyl Alcohol. This polymer mixture was sprayed onto the tablets in a conventional pan coater to obtain film-coated tablets which membrane coating weighed 29.4 mg approximately. A 0.50-mm hole was drilled through the coating in one face of the tablet.

The third composition was prepared by mixing 4.39 g of Copolyvidone, 3.94 g of Titanium Dioxide, 14.17 g of Talc and 9.00 mg of Aluminum Lake Brilliant Blue in Isopropyl Alcohol. This polymer mixture was sprayed onto the tablets in a conventional pan coater to obtain film-coated tablets which membrane coating weighed 15 mg approximately.

The rapid release external coating was prepared by mixing 5.00 g of Risperidone, 381.00 g of Microcrystalline Cellulose, 32.00 g of Povidone, 20.50 g of Crospovidone and 3.00 g of Colloidal Silicon Dioxide. The mixture was blended to homogeneity; then, 8.50 g of Magnesium Stearate was added as lubricant. This blend was compressed over the film-coated tablets using biconcaves, 14.0-mm diameter punches. Coating weight: 450 mg. Hardness from 8 to 12 kp.

The final coating was prepared by mixing 22.68 g of Hydroxypropyl methylcellulose 2910, 6.47 g of Polyethylene Glycol 6000, 8.31 g of Titanium Dioxide and 45.00 mg of Aluminum Lake Red Ponceau in a mixture of Methylene Chloride-Alcohol 96° 70:30 v/v (volume/volume). This polymer mixture was sprayed onto the tablets in a conventional pan coater to obtain film-coated tablets which membrane coating weighed 25 mg approximately.

Tablets made according to the above procedure generally have the following formulation.

CORE	
Venlafaxine Hydrochloride	84.860 mg
Mannitol	238.830 mg
Povidone	25.00 mg
Polyethylene Glycol 400	1.500 mg
Colloidal Silicon Dioxide	3.000 mg
Polyethylene Glycol 6000	22.310 mg
Magnesium Stearate	4.500 mg

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COATING A

Copolyvidone	7.530 mg
Hydroxypropyl methylcellulose 2910	10.500 mg
Polyethylene Glycol 6000	3.000 mg
Titanium Dioxide	3.970 mg

COATING B

Cellulose Acetate	27.930 mg
Polyethylene Glycol 400	1.470 mg

COATING C

Copolyvidone	2.925 mg
Titanium Dioxide	2.625 mg
Talc	9.444 mg
Aluminum Lake brilliant Blue	0.006 mg

COATING D

Risperidone	5.000 mg
Microcrystalline Cellulose	381.000 mg
Povidone	32.000 mg
Crospovidone	20.500 mg
Colloidal Silicon Dioxide	3.000 mg
Magnesium Stearate	8.500 mg

COATING E

Hydroxypropyl methylcellulose 2910	15.120 mg
Polyethylene Glycol 6000	4.310 mg
Titanium Dioxide	5.540 mg
Aluminum Lake Red Ponceau	0.030 mg

EXAMPLE 3

The following general method was used to administer the osmotic device of the invention to human patients and to evaluate the performance of the osmotic device of the invention to that of the EFFEXOR XR capsule. The bioavailability of the osmotic device was evaluated using a two-period, single-dose, cross-over randomized pharmacokinetic study with a one-week washout period using EFFEXOR XR as the control product. Twelve healthy hospitalized subjects (non-smokers between the ages of 21-50) were randomly separated into two equally sized groups. The first group received the formulation of Example 1 (75 mg of venlafaxine) and the second group received the control formulation thirty minutes after a normal breakfast during the first period. After the washout period, the

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first group received the control formulation and the second group received the formulation of Example 1 during a second period. Blood samples were taken periodically from 0 to 48 hrs after administration and plasma aliquots were obtained immediately and stored at -20° C for later analysis by HPLC to determine VFX content. The following pharmacokinetic parameters were calculated from the plasma concentration curve for each formulation and each subject: area under the curve from 0-48 hrs (AUC_{0-48}) and extrapolated to infinity ($AUC_{0-\infty}$); maximum concentration of VFX in plasma (C_{max}); and time to reach C_{max} (T_{max}). Safety was evaluated by physical examination, vital signs and adverse event records. Statistical comparisons were made using Analysis of Variance (ANOVA) for the crossover design. Geometric means and classical 90% confidence intervals for the ratio (test/control) of means were calculated in order to evaluate bioequivalence.

EXAMPLE 4

The following general formulation was used to make an osmotic device according to Example 1, which has a dissolution profile similar to that depicted in FIG. 1 and provides a plasma profile similar to that depicted in FIG. 2.

INGREDIENT	Amount (mg)
<i>CORE</i>	
Venlafaxine (salt or free form)	10-500
Osmagent	350-500
Binder	15-100
Plasticizer (lower molecular weight)	0.1-50
Glidant	0.1-12
Plasticizer (higher molecular weight)	5-60
Lubricant	2-15
<i>COATING A</i>	
First water soluble polymer	8-15
Second water soluble polymer	5-25
Plasticizer (higher molecular weight)	0.2-4
Opaquant	0.1-12
<i>COATING B</i>	
Cellulose ester	40-75
Plasticizer (lower molecular weight)	0.5-13
<i>COATING C</i>	
Second water soluble polymer	5-30

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Third water soluble polymer	3-15
Plasticizer (higher molecular weight)	1-6
Opaquant	2-8
First Colorant	0.01-0.1
Second Colorant	0.001-0.05

EXAMPLE 5

The following general formulation was used to make an osmotic device according to Example 2, which has a dissolution profile similar to that depicted FIG. 1 and provides a plasma profile similar to that depicted in FIG. 2.

INGREDIENT	Amount (mg)
<i>CORE</i>	
Venlafaxine (salt or free form)	10-500
Osmagent	175-250
Binder	7.5-50
Plasticizer (lower molecular weight)	0.1-25
Glidant	0.1-6
Plasticizer (higher molecular weight)	2.5-30
Lubricant	1-7.5
<i>COATING A</i>	
First water soluble polymer	4-7.5
Second water soluble polymer	2.5-12.5
Plasticizer (higher molecular weight)	0.1-2
Opaquant	0.1-6
<i>COATING B</i>	
Cellulose ester	20-37.5
Plasticizer (lower molecular weight)	0.1-6.5
<i>COATING C</i>	
First water soluble polymer	0.5-5
First opaquant	0.1-10
Second opaquant	1.0-15
Colorant	0.001-0.05
<i>COATING D</i>	
Risperidone	0.25-20
Filler	280-500
Binder	15-60
Disintegrant	12-70
Glidant	0.1-9

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Lubricant	0.5-12
<i>COATING E</i>	
Second water soluble polymer	8-30
Plasticizer (higher molecular weight)	0.5-8
Opaquant	2-10
Colorant	0.01-0.05

The above is a detailed description of particular embodiments of the invention. It is recognized that departures from the disclosed embodiments may be made within the scope of the invention and that obvious modifications will occur to a person skilled in the art. Those of skill in the art should, in light of the present disclosure, appreciate that many changes can be made in the specific embodiments which are disclosed herein and still obtain a like or similar result without departing from the spirit and scope of the invention. All of the embodiments disclosed and claimed herein can be made and executed without undue experimentation in light of the present disclosure.

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CLAIMS

We claim:

1. An osmotic device for the delivery of venlafaxine and an anti-psychotic agent comprising:
 - 5 a core comprising a therapeutically effective amount of VFX and at least one osmotic agent or osmopolymer;
 - a semipermeable membrane surrounding the core and having a passageway there through; and
 - an external coat comprising a therapeutically effective amount of an anti-psychotic agent;
 - 10 wherein the core provides a controlled release of VFX, and at least 80% of the VFX is released within 13 hours after exposure of the osmotic device to an aqueous solution, and the external coat provides a rapid release of the anti-psychotic agent, and at least 75% of the anti-psychotic agent is released within 1 hour after exposure of the
 - 15 osmotic device to an aqueous solution.
2. The osmotic device of claim 1, wherein the external coat is applied by spraying a composition onto the semipermeable membrane.
3. The osmotic device of claim 1, wherein the external coat is compressed about and surrounds the semipermeable membrane.
- 20 4. The osmotic device of claim 1, wherein at least 75% of the anti-psychotic agent is released within about 40 minutes, and at least about 60% of the VFX is released within about 12 hours after administration.
5. The osmotic device of claim 1, wherein the release of at least one of the VFX and the anti-psychotic agent has a delayed onset.
- 25 6. The osmotic device of claim 1, wherein the anti-psychotic agent is selected from the group consisting of risperidone, olanzapine, clozapine, sertindole, ziprasidone, quetiapine, sulpiride, pimozide, clothiapine, molindone, loxapine, trifluoperazine, haloperidol, flupenthixol, chlorpromazine, chlorprothixene, clopenthixol, droperidol, perphenazine, fluphenazine, lithium, mesoridazine, spiperone,
- 30 promazine, prochlorperazine, thioridazine, thiothixene, triflupromazine and raclopride.

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7. The osmotic device of claim 6, wherein the venlafaxine is administered once daily at a dose of 10-500 and the anti-psychotic agent is administered once daily at a dose of: a) risperidone- 5 to 10 mg per day; b) olanzapine- 5 to 20 mg, 0.25-50 mg, 1-30 mg, or 1-25 mg per day; c) clozapine- 100 to 400 mg, 12.5-900 mg, or 150-450 mg per day; d) sertindole- 15 to 20 mg per day or 0.0001 to 1.0 mg/kg of body weight per day; e) ziprasidone- 80 to 160 mg, 5 to 500 mg or 50 to 100 mg per day; f) quetiapine- 150 to 600 mg or 1.0-40 mg/kg of body weight per day; g) sulpiride- 50 to 100 mg per day; h) pimozide- 2 to 4 mg per day; or i) clothiapine- 40 mg per day.
8. The osmotic device of claim 1, wherein the osmotic device delivers the anti-psychotic agent to the upper GI tract and the venlafaxine to the middle to lower GI tract.
9. The osmotic device of claim 1, wherein the osmotic device provides a VFX C_{max} of about 17-23 ng/ml of plasma in a mammal.
10. The osmotic device of claim 9, wherein the osmotic device provides a VFX T_{max} at about 7-11 hours.
11. The osmotic device of claim 1, wherein the osmotic device provides a VFX dissolution profile as follows:

Time (h)	Released (%)	STD (%)
1	7.2	1.3
3	23.6	0.5
5	43.3	2.1
7	59.0	2.3
9	69.7	2.1
11	77.0	1.8
13	81.8	1.7
15	84.7	1.7
19	88.1	1.4
23	≥90.8	1.5

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12. The osmotic device of claim 11, wherein the osmotic device provides a single-dose VFX plasma concentration profile in a mammal as follows:

Time (h)	Mean VFX Plasma Concentration (ng/ml)	S.E.M.
0	0.0	0.0
0.5	0.3	0.2
1	0.4	0.2
2	3.2	0.8
4	13.9	2.6
6	17.5	2.5
8	18.7	2.7
10	18.8	2.9
12	16.7	2.5
14	15.8	2.7
16	11.8	2.0
20	8.6	1.7
24	6.6	1.1
28	5.7	1.5
32	3.4	0.7
36	2.2	0.5
48	1.7	0.5

13. The osmotic device of claim 1, wherein the osmotic device provides a VFX $C_{\max}$ of about 20-27 ng/ml of plasma in a mammal.
14. The osmotic device of claim 13, wherein the osmotic device provides a VFX $T_{\max}$ at about 3.5-8.5 hours.
15. The osmotic device of claim 1, wherein the osmotic device provides a VFX release profile as follows:

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Time (h)	Mean Released (%)	S.D. (%)
0	0	0
0.5	0.13	0.44
1	1.43	1.93
2	10.61	8.37
4	40.48	5.44
6	54.27	4.78
8	63.13	4.67
10	66.59	3.36
12	71.44	5.81
14	76.09	5.92
16	77.65	6.58
20	84.94	6.58
24	≥89.43	6.48

16. The osmotic device of claim 15, wherein the osmotic device provides a single-dose VFX plasma concentration profile in a mammal as follows:

Time (h)	Mean VFX Plasma Concentration (ng/ml)	S.E.M.
0	0	0
0.5	0.2	0.2
1	1	0.4
2	6	1.6
4	21.2	3.1
6	22.6	3.3
8	21.3	4.0
10	16.8	2.9
12	15.4	3.3
14	13.4	2.8
16	9.6	1.5

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Time (h)	Mean VFX Plasma Concentration (ng/ml)	S.E.M.
20	8.9	2.5
24	6.5	1.5
28	4.6	1.1
32	3.7	1.0
36	3.1	0.9
48	1.3	0.3

17. The osmotic device of claim 1, wherein the osmotic device further comprises a first water soluble coat between the core and the semipermeable membrane.

18. The osmotic device of claim 17 comprising the following ingredients in the approximate amounts indicated:

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INGREDIENT	Amount (mg)
<i>Core</i>	
Venlafaxine (salt or free form)	10-500
Osmagent	350-500
Binder	15-100
Plasticizer (lower molecular weight)	0.1-50
Plasticizer (higher molecular weight)	5-60
<i>First water soluble coat</i>	
First water soluble polymer	8-15
Second water soluble polymer	5-25
Plasticizer (higher molecular weight)	0.2-4
<i>Semipermeable membrane</i>	
Cellulose ester	40-75
Plasticizer (lower molecular weight)	0.5-13
<i>External coat</i>	
Second water soluble polymer	5-30
Third water soluble polymer	3-15
Plasticizer (higher molecular weight)	1-6

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19. The osmotic device of claim 17 further comprising a second water soluble coat between the semipermeable membrane and the external coat and an optional exterior finish coat.

20. The osmotic device of claim 19 comprising the following ingredients in the approximate amounts indicated:

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INGREDIENT	Amount (mg)
<i>Core</i>	
Venlafaxine (salt or free form)	10-500
Osmagent	175-250
Binder	7.5-50
Plasticizer (lower molecular weight)	0.1-25
Plasticizer (higher molecular weight)	2.5-30
<i>First water soluble coat</i>	
First water soluble polymer	4-7.5
Second water soluble polymer	2.5-12.5
Plasticizer (higher molecular weight)	0.1-2
<i>Semipermeable membrane</i>	
Cellulose ester	20-37.5
Plasticizer (lower molecular weight)	0.1-6.5
<i>Second water soluble coat</i>	
First water soluble polymer	0.5-5
First opaquant	0.1-10
Second opaquant	1.0-15
<i>External coat</i>	
Risperidone	0.25-20
Filler	280-500
Binder	15-60
Disintegrant	12-70
<i>Optional exterior finish coat</i>	
Second water soluble polymer	8-30
Plasticizer (higher molecular weight)	0.5-8

21. A method of treating depression, anxiety and/or psychosis in a mammal, the method comprising the step of administering an osmotic device according to any one of claims 1-20.

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FIG. 1

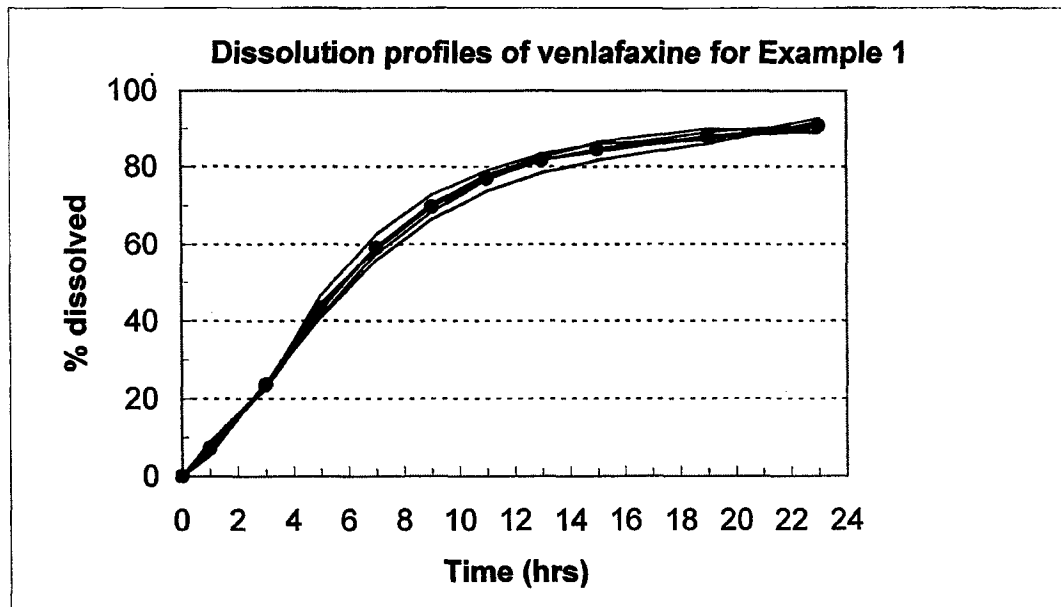
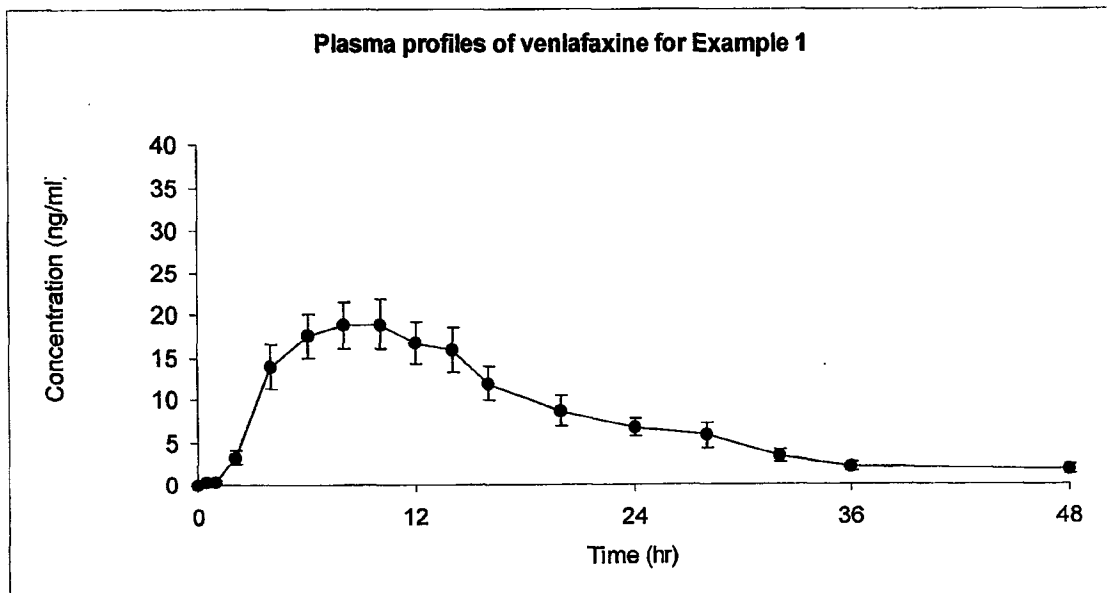


FIG. 2



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FIG. 3

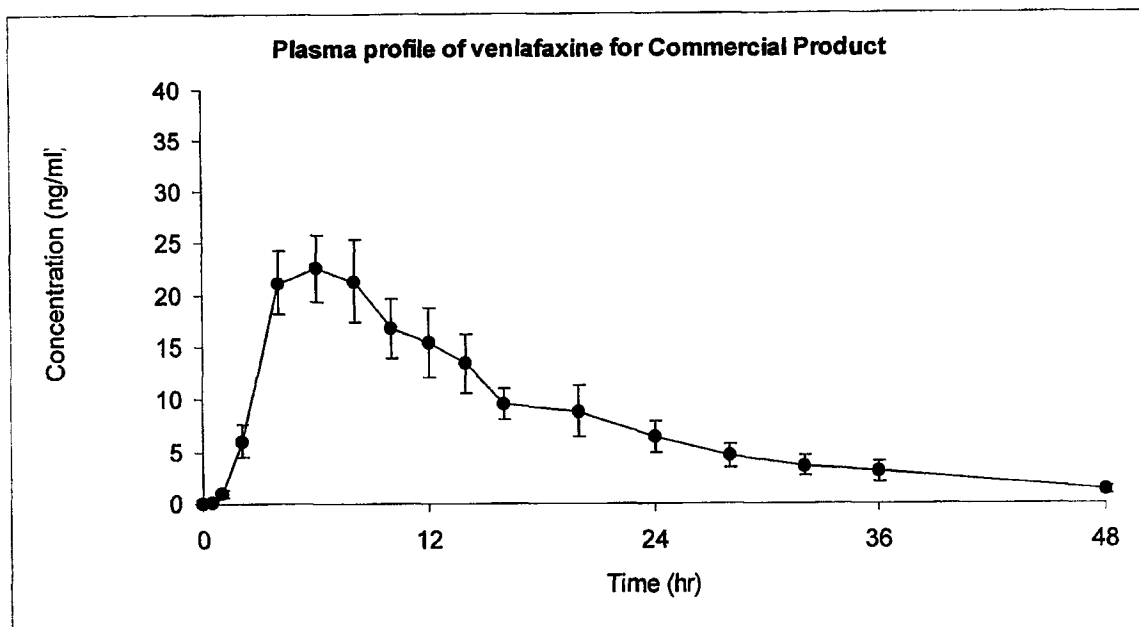
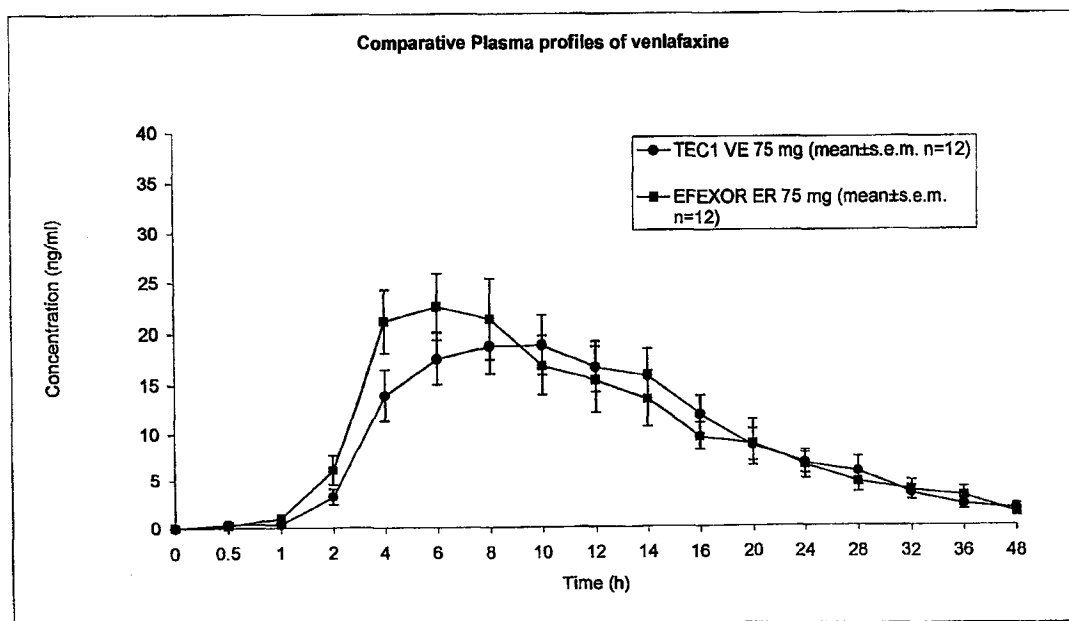


FIG. 4



INTERNATIONAL SEARCH REPORT

International application No.
PCT/US01/00580

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A61K 9/48, 9/52, 9/58, 9/60, 9/62, 9/64, 9/28

US CL : 424/451, 452, 457, 462, 464, 465, 468, 471, 472, 473, 474

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/451, 452, 457, 462, 464, 465, 468, 471, 472, 473, 474

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EAST

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A,P	US 6,147,072 A (BYMASTER et al.) 14 November 2000, see entire document.	1-21
A,P	US 6,096,742 A (CROCKER et al.) 01 August 2000, see entire document.	1-21
A,P	US 6,060,642 A (TECOTT et al.) 09 May 2000, see entire document.	1-21

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A" document defining the general state of the art which is not considered to be of particular relevance	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E" earlier document published on or after the international filing date	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"A" document member of the same patent family
"O" document referring to an oral disclosure, use, exhibition or other means	
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search 27 FEBRUARY 2001	Date of mailing of the international search report 03 MAY 2001
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer LILIANA DI NOLA-BARON Telephone No. (703) 308-1235

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US 20020151543A1

(19) **United States**(12) **Patent Application Publication**
Barberich et al.(10) **Pub. No.: US 2002/0151543 A1**(43) **Pub. Date: Oct. 17, 2002**(54) **COMPOSITIONS AND METHODS
EMPLOYING R (-) FLUOXETINE AND
OTHER ACTIVE INGREDIENTS**(75) Inventors: **Timothy J. Barberich**, Concord, MA
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WASHINGTON, DC 20006(73) Assignee: **Sepracor Inc.**, Marlborough, MA(21) Appl. No.: **10/158,886**(22) Filed: **Jun. 3, 2002****Related U.S. Application Data**(60) Division of application No. 09/664,732, filed on Sep.
19, 2000, now abandoned, which is a continuation-in-part of application No. 09/177,703, filed on Oct.
23, 1998, now abandoned, which is a continuation-
in-part of application No. 09/086,262, filed on May
28, 1998, now abandoned.**Publication Classification**(51) **Int. Cl.⁷ A61K 31/5513; A61K 31/137**
(52) **U.S. Cl. 514/221; 514/651**(57) **ABSTRACT**

Pharmaceutical compositions which comprises R(-) fluoxetine and one or more other biologically active compounds are disclosed. Methods of treating or preventing a disease or disorder, especially a psychotic or psychiatric disease or disorder, using the above pharmaceutical composition or by administering a R(-) fluoxetine in combination with one or more other biologically active compounds are also disclosed. Methods of treating patients having or at risk of having AIDS or HIV infection, cancer, cardiac disorder, post-myocardial depression and posttraumatic stress disorder using optically pure R(-) fluoxetine in combination with one or more other biologically active compounds are further disclosed.

COMPOSITIONS AND METHODS EMPLOYING R(-) FLUOXETINE AND OTHER ACTIVE INGREDIENTS

[0001] This application is a continuation-in-part of the U.S. patent application Ser. No. 09/086,262, filed May 28, 1998, the content of which is incorporated herein by reference.

FIELD OF THE INVENTION

[0002] This invention relates to pharmaceutical compositions and methods of treatment or prevention employing two or more active ingredients.

INTRODUCTION

[0003] The present invention encompasses pharmaceutical compositions which comprise, and methods which utilize, optically pure R(-) fluoxetine and a second biologically active compound, preferably, a benzodiazepine compound, a tricyclic antidepressant, a 5-HT_{1A} receptor antagonist, a 5-HT₂ receptor agonist, a β -adrenergic antagonist, an antipsychotic agent, an anti-anxiolytic or other psychotropic drug. The present invention is well suitable for treating patients, having AIDS or HIV infection, cancer, cardiac disorder, post-myocardial depression, posttraumatic stress disorder or psychiatric disorder.

BACKGROUND OF THE INVENTION

[0004] Fluoxetine, N-methyl-3-phenyl-3-[(α,α,α -trifluoro-p-tolyl)-oxy]-propylamine, is marketed as the hydrochloride salt form of the racemic mixture under the trade-name PROZAC® (U.S. Pat. No. 4,314,081). PROZAC® is indicated for the treatment of depression, obsessive-compulsive disorder (OCD) and bulimia nervosa (Physician's Desk References® 52 Edition 1998, pages 859-860).

[0005] As disclosed in U.S. Pat. No. 5,708,035, the racemic mixture of fluoxetine has certain disadvantages including headaches, nervousness, anxiety, insomnia, akathisia, severe anxiety leading to intense violent suicidal thoughts and self mutilation, manic behavior, nausea, diarrhea, drowsiness, decrease in libido, and/or sexual dysfunction. The major disadvantage of the racemic mixture of fluoxetine is its long half-life and long duration of action. This long half life can lead to a buildup of fluoxetine in the patient's body and a concomitant increase in the above described side effects when a patient is given multiple doses. More importantly, its long half-life and long duration of action also makes it impossible or impractical to use the racemic mixture of fluoxetine as part of a combination therapy, although combination therapy might be very desirable.

[0006] R(-) fluoxetine, and its use, is described in U.S. Pat. Nos. 5,708,035 and 5,648,396 to Young et al. These patents state that the use of R(-) fluoxetine decreases the incidence of adverse effects seen with the racemic mixture of fluoxetine. These patents also state that R(-) fluoxetine is useful in the treatment of depression, migraine headaches, pain, in particular chronic pain, psychoactive substance abuse disorders and obsessive compulsive disorders. Additionally, U.S. Pat. No. 5,648,396 discloses a method of treating depression in a human by first administering R(-) fluoxetine followed by a subsequent administration of a monoamine oxidase inhibitor.

[0007] U.S. Pat. No. 5,356,934 discloses a method for treating sleep apnea in mammals which comprises administering to mammal requiring sleep apnea treatment an effective amount of (R)-fluoxetine or a pharmaceutically acceptable acid addition salt or solvate thereof.

[0008] U.S. Pat. No. 4,035,511 discloses a method of producing analgesia or reducing hyperalgesia by administering racemic fluoxetine either alone or with morphine sulfate.

[0009] U.S. Pat. No. 4,329,356 discloses a method for lowering blood pressure in a hypertensive mammal which comprises the co-administration of racemic fluoxetine and 1-5-hydroxytryptophane, or preferably the co-administration of fluoxetine, 1-5-hydroxytryptophane and a peripheral decarboxylase inhibitor such as carbidopa[α -hydrazino- α -methyl- β -(3,4-dihydroxyphenyl) propionic acid monohydrate] or banserazide [n-(dl-seryl)-nu"-(2,3,4-trihydroxybenzyl)hydrazine].

[0010] U.S. Pat. No. 4,594,358 and U.S. Pat. No. 4,683,235 discloses, respectively, a method of potentiating dextropropoxyphene or codeine analgesia in mammals, either alone or in combination with aspirin or acetaminophen, which comprises the administration of an effective amount of racemic fluoxetine or norfluoxetine prior to, concomitantly with, or after the administration of dextropropoxyphene or codeine which, if given alone, would produce less than the desired analgesic effect.

[0011] U.S. Pat. No. 4,895,845 discloses a method of assisting weight loss in patients through the concomitant administration of a rauwolfia alkaloid and at least one antidepressant selected from the group consisting of aminoazoles, phenoxyphenylpropylamine antidepressants such as fluoxetine, and aminopropiophenones, or preferably through the concomitant administration of a rauwolfia alkaloid, at least one antidepressant selected from the group consisting of aminoazoles, phenoxyphenylpropylamines, and aminopropiophenones, and one or more of the sympathomimetic anorectic agents that have proved successful in some instances in promoting patient compliance to a calorically-restricted diet.

[0012] U.S. Pat. No. 5,512,593 discloses a method of treating depression comprising administering to a patient an opioid antagonist selected from the group consisting of naltrexone, naloxone and a compound selected from the group consisting of one or more non-tricyclic antidepressants exhibiting serotonin reuptake inhibition in the synapses of the central nervous system such as bupropion, sertraline, fluoxetine, and trazodone.

[0013] U.S. Pat. No. 5,527,788 discloses the use of DHEA and at least one anorectic agent, such as fenfluramine HCl, phentermine HCl, phendimetrazine tartrate, mazindol, diethylpropion HCl, and fluoxetine HCl, in combination to produce weight loss in animals.

[0014] U.S. Pat. No. 5,532,268, U.S. Pat. No. 5,538,992 and U.S. Pat. No. 5,552,429 discloses, respectively, a method for potentiating the action of fluoxetine, in increasing the availability of serotonin, norepinephrine and dopamine in the brain, comprising administering fluoxetine to a patient in need thereof in combination with a second component which is chosen from the group consisting of alpre-

nolol, WAY 100135, spiperone, propranolol and tertatolol, pindolol, or a compound of the formula I that is described therein.

[0015] WO 92/00103 discloses a pharmaceutical product comprising two or three active ingredients selected from a 5-HT₁ receptor antagonist, a 5-HT re-uptake inhibitor such as fluoxetine and a 5-HT₁ receptor agonist, as a combined preparation for simultaneous, separate or sequential use in therapy of depression and/or migraine.

[0016] WO 96/09044 discloses compositions for the effective treatment of a variety of chronic and intractable disorders, such as intractable coughing, dermatitis, chronic pain and tinnitus, which failed to respond to other treatments. The compositions are a therapeutically effective dosage of dextromethorphan (DM) in combination with a therapeutically effective dosage of an inhibitor of enzymatic dextromethorphan oxidation by the liver enzyme debrisoquin hydroxylase. As disclosed therein, antioxidants include yohimbine, fluoxetine, haloperidol, ajmaline, lobeline, pipamperone.

[0017] WO 96/09047 discloses a method of treating alcoholism and alcohol dependence in a mammal comprising administering to the mammal a therapeutically effective amount of a synergistic combination of at least one opioid antagonist, and at least one selective serotonin reuptake inhibitor. The phrase "selective serotonin reuptake inhibitor", as used therein, denotes compounds which enhance brain serotonergic activity by blocking the neuronal reuptake and subsequent inactivation of serotonin at synaptic junctions between nerve cells; such include fluoxetine, sertraline, paroxetine, venlafaxine, fluvoxamine, nefazodone, citalopram, and zimeldine.

[0018] WO 97/31629 discloses a method of treating disorders of sleep comprising administering to a patient in need of such treatment a first component chosen from the group consisting of fluoxetine, venlafaxin, citalopram, fluvoxamine, paroxetine, milnacipran and duloxetine in combination with a second component chosen from the group consisting of alprenolol, WAY 100135, WAY 100635, spiperone, pindolol, (S)-UH-301, penbutolol, propranolol, tertatolol, and a compound of the formula I as described therein.

[0019] From the above, it appears that the art has been exploring the use of racemic fluoxetine in combination with other drugs for a number of uses. However, there is a need for combination therapy with the advantages of racemic fluoxetine without the disadvantages of racemic fluoxetine such as the great potential for adverse drug-drug interactions.

SUMMARY OF THE INVENTION

[0020] The present invention encompasses a pharmaceutical composition which comprises an effective amount of optically pure R(-) fluoxetine, or a pharmaceutically acceptable salt thereof, substantially free of its S(+) stereoisomer, an effective amount of second biologically active compound and a pharmaceutically acceptable carrier. The present invention also relates to a method of treating or preventing diseases or disorders in humans, especially a psychotic or psychiatric disease or disorder, using such pharmaceutical compositions.

[0021] The present invention also encompasses a method of treating or preventing a psychotic or psychiatric disease

or disorder by administering optically pure R(-) fluoxetine and a second biologically active compound, preferably a benzodiazepine compound, a tricyclic antidepressant, an antipsychotic agent, an anti-anxiolytic, a β -adrenergic antagonist, a 5-HT_{1A} receptor antagonist, a 5-HT₃ receptor agonist, or a compound selected from the group consisting of buspirone, hydroxyzine, lorazepam, olanzapine, quetiapine, risperidone, 9-hydroxy-risperidone, sertindole, tomoxetine, valium and ziprasidone. The present invention further encompasses methods of treating patients, having or at risk of having AIDS or HIV infection, cancer, cardiac disorder, post-myocardial depression, posttraumatic stress disorder or other psychiatric disorders, using optically pure R(-) fluoxetine in combination with one or more biologically active compounds.

[0022] Finally, the present invention encompasses methods of treating or preventing a psychotic or psychiatric disease or disorder which comprises administering an effective amount of R(-) fluoxetine and an amount of a biologically active 5-HT_{1A} receptor antagonist for a first period of time, and after the first period of time, administering an effective amount of R(-) fluoxetine and a reduced amount of said biologically active 5-HT_{1A} receptor antagonist for a second period of time; and kits to be used for such treatment or prevention.

[0023] Thus, the invention encompasses the use of R(-) fluoxetine, salts, solvates, hydrates and pro-drugs thereof in combination with one or more additional active ingredients. R(-) fluoxetine can be used in the same pharmaceutical composition as the one or more additional active ingredient, or R(-) fluoxetine can be administered concurrently or sequentially with the other active ingredients, i.e., before, during or after.

[0024] The present invention does not contemplate a pharmaceutical composition containing an effective amount of optically pure R(-) fluoxetine and an effective amount of a monoamine oxidase inhibitor. The present invention also does not encompass methods of treatment or prevention using optically pure R(-) fluoxetine in combination with a monoamine oxidase inhibitor.

[0025] Specific preferred combinations and further details of the invention are described in detail below.

THE DETAILED DESCRIPTION OF THE INVENTION

[0026] The present invention encompasses pharmaceutical compositions which comprise a therapeutically effective amount of R(-) fluoxetine or a pharmaceutically acceptable salt thereof, substantially free of its S(+) stereoisomer, an effective amount of second biologically active compound, preferably, a benzodiazepine compound, a tricyclic antidepressant, an antipsychotic agent, a 5-HT_{1A} receptor antagonist such as pindolol, a 5-HT₃ receptor agonist, a β -adrenergic antagonist such as pindolol, an anti-anxiolytic, or a compound selected from the group consisting of buspirone, hydroxyzine, lorazepam, olanzapine, quetiapine, risperidone, 9-hydroxy-risperidone, sertindole, tomoxetine, valium and ziprasidone, and a pharmaceutically acceptable carrier.

[0027] Any pharmaceutically acceptable salt of R(-) fluoxetine can be used in the present invention; however, acid addition salts are preferred. The most preferred pharmaceutically acceptable salt of R(-) fluoxetine is the hydrochloride salt.

[0028] The compositions and methods of this invention employ the optically pure R(-) isomer of fluoxetine in combination with drugs that act on the central nervous system ("CNS"), such as 5-HT_{1A} receptor, including hypnotics and sedatives; drugs useful in treating psychiatric disorders, such drugs include antipsychotic or neuroleptic drugs, antianxiety drugs, antidepressants and mood-stabilizers; central nervous system stimulants such as amphetamines; dopamine receptor agonists; antimonoclonal agents; antipanic agents; and antipsychotic agents and the like. R(-) fluoxetine may also be used in combination with cardiovascular agents (beta blockers and ACE inhibitors); antivirals; antibiotics, antifungals; antineoplastics; and others.

[0029] The present invention provides the skilled artisan with a substantial benefit, that is, the ability to use a SSRI compound, such as R(-) fluoxetine, with one or more other active drugs without, or with reduced concern for, adverse drug-drug interactions. For example, R(-) fluoxetine can be used in a number of different patient populations including but not limited to cancer patients, cardiac patients, AIDS patients or HIV infected populations, and psychiatric patients, each of which is likely undergoing treatment with a drug other than racemic fluoxetine or its enantiomers. Further, many patients afflicted with life threatening diseases experience depression particularly at or about the time they first learned of their affliction. For example, victims of heart attacks are known to experience depression. Now these patients can be treated for their cardiac disorder as well as be treated for their depression while avoiding the adverse effects associated with the administration of racemic fluoxetine.

[0030] Moreover, the use of R(-) fluoxetine in combination with the drugs described herein provides an improved therapy over certain therapies presently available in the art; the use of R(-) fluoxetine and certain of the drugs may allow for treatment where none was previously available; and certain combinations can provide a synergistic benefit.

[0031] In a preferred embodiment, R(-) fluoxetine is used in combination with a benzodiazepine compound, a tricyclic antidepressant, an antipsychotic agent, an anti-anxiolytic, a β -adrenergic antagonist, a 5-HT_{1A} receptor antagonist, a 5-HT₃ receptor agonist, or one or more of the following compounds: buspirone, hydroxyzine, lorazepam, olanzapine, quetiapine, risperidone, 9-hydroxy-risperidone, sertindole, tomoxetine, valium and ziprasidone.

[0032] The preferred benzodiazepine compounds for use within the present invention include, but are not limited to, alprazolam, brotizolam, chlordiazepoxide, clobazam, clonazepam, clorazepate, demoxepam, diazepam, estazolam, flumazenil, flurazepam, halazepam, lorazepam, midazolam, nitrazepam, nordazepam, oxazepam, prazepam, quazepam, temazepam or triazolam.

[0033] The preferred tricyclic antipsychotic compounds for use within the present invention include, but are not limited to, chlorpromazine, mesoridazine, thioridazine, acetophenazine, fluphenazine, perphenazine, trifluoperazine, chlorprothixene, thiothixene, clozapine, haloperidol, loxapine, molindone, pimozone, risperidone, 9-hydroxy-risperidone or desipramine.

[0034] The preferred 5-HT_{1A} receptor antagonists for use within the present invention include, but are not limited to,

alprenolol, WAY 100135, spiperone, pindolol, (S)-UH-301, penbutolol, propranolol, tertatolol, and a compound of the formula I as disclosed in U.S. Pat. No. 5,552,429, the content of which is herein incorporated by reference.

[0035] In a preferred embodiment, a pharmaceutical composition of the invention comprises from about 5 mg to about 100 mg of R(-) fluoxetine, and the second biologically active compound, which is a benzodiazepine compound, a tricyclic antidepressant, an antipsychotic agent, an anti-anxiolytic, a β -adrenergic antagonist, a 5-HT_{1A} receptor antagonist, a 5-HT₃ receptor agonist, or a compound selected from the group consisting of buspirone, hydroxyzine, lorazepam, olanzapine, quetiapine, risperidone, 9-hydroxy-risperidone, sertindole, tomoxetine, valium and ziprasidone. The dosage of the second biologically active compound can be easily determined by skilled artisans, e.g., following dosages recommended in the Physician's Desk Reference® 52 Edition 1998.

[0036] In a preferred pharmaceutical composition, the R(-) fluoxetine is present in an amount on weight basis, relative to S(+) fluoxetine, from about 100:1 to about 10,000:1.

[0037] The present invention also relates to a method of treating or preventing a disease or disorder, especially a psychotic or psychiatric disease or disorder, using the above pharmaceutical composition.

[0038] The present invention further encompasses methods of treating or preventing a disease or disorder by administering R(-) fluoxetine in combination with a second biologically active compound which is a benzodiazepine compound, a tricyclic antidepressant, an anti-anxiolytic, a β -adrenergic antagonist, a 5-HT_{1A} receptor antagonist, a 5-HT₃ receptor agonist, or a compound selected from the group consisting of buspirone, hydroxyzine, lorazepam, olanzapine, quetiapine, risperidone, 9-hydroxy-risperidone, sertindole, tomoxetine, valium and ziprasidone.

[0039] The diseases or disorders that can be treated or prevented using R(-) fluoxetine and a benzodiazepine include, but are not limited to, depression, anxiety, alcohol withdrawal, preoperative apprehension, Lennox-Gastaut syndrome (petit mal variant), bulimia nervosa, seizures, bipolar disorders, panic disorder, skeletal muscle spasm, spasticity caused by upper motor neuron disorders, athetosis and stiffman syndrome, convulsive disorders and insomnia.

[0040] The diseases or disorders that can be treated or prevented using R(-) fluoxetine and a tricyclic antipsychotic compound include, but are not limited to, anxiety, depression, nausea, vomiting, restlessness and apprehension before surgery, acute intermittent porphyria, tetanus, intractable hiccups, severe behavioral problems and hyperactivity in children, emotional withdrawal, conceptual disorganization, tension, hallucinatory behavior, suspiciousness and blunted affect in schizophrenic patients or Tourette's Disorder.

[0041] The diseases or disorders that can be treated or prevented using R(-) fluoxetine and a 5-HT_{1A} receptor antagonist include, but are not limited to, depression, obsessive-compulsive disorders, obesity and late luteal phase syndrome, hypertension, migraine, essential tremor, hypertrophic subaortic stenosis and pheochromocytoma. The more preferred disease or disorder that can be treated or

prevented using R(-) fluoxetine and a 5-HT_{1A} receptor antagonist includes, but is not limited to, posttraumatic depression disorder.

[0042] The diseases or disorders that can be treated or prevented using R(-) fluoxetine and a compound selected from the group consisting of buspirone, hydroxyzine, lorazepam, olanzapine, quetiapine, risperidone, 9-hydroxy-risperidone, sertindole, tomoxetine, valium and ziprasidone include, but are not limited to, anxiety, Attention Deficit Disorders, depression, hypertension, schizophrenia and psychotic disorders.

[0043] The disease or disorder that can be treated or prevented using R(-) fluoxetine and a β -adrenergic antagonist includes, but is not limited to, post myocardial infarction depression. The preferred β -adrenergic antagonists include, but are not limited to, S(-) pindolol, penbutolol and propranolol.

[0044] As used in the present application, the terms "substantially free of the S(+) stereoisomer" and "optically pure R(-) fluoxetine" means that the composition contains at least 90% by weight of R(-) fluoxetine and 10% by weight or less of S(+) fluoxetine. In the most preferred embodiment the "substantially free of the S(+) stereoisomer" means that the composition contains at least 99% by weight R(-) fluoxetine and 1% or less of S(+) fluoxetine.

[0045] Optically pure R(-) fluoxetine can be asymmetrically synthesized or it can be resolved using conventional techniques, both of which are known in the art. For example, the synthesis of R(-) isomer of fluoxetine is disclosed in U.S. Pat. Nos. 5,648,396 and 5,708,035, the contents of which are incorporated by reference.

[0046] Unless otherwise indicated herein, when the name of a chiral drug is used without modification that name refers to the racemic mixture, the (+) and (-) isomers and mixtures thereof. For example, "pindolol" refers to racemic pindolol, S(+) pindolol, R(-) pindolol and mixtures of S(+) and R(-) pindolol.

[0047] The term benzodiazepine refers to the portion of the structure composed of a benzene ring (A) fused to a seven-membered diazepine ring (B) (Goodman & Gilman, *The Pharmacological Basis of Therapeutics*, 9th Ed. McGraw-Hill, 1996, Chapter 17, p 363). However, since all the important benzodiazepines contain a 5-aryl substituent (ring C) and a 1,4-diazepine ring, the term has come to mean the 5-aryl-1,4-benzodiazepines. Various modifications in the structure of the ring systems have yielded compounds with similar activities.

[0048] The effects of the benzodiazepines virtually all result from actions of these drugs on the CNS. The most prominent of these effects are sedation, hypnosis, decreased anxiety, muscle relaxation, anterograde amnesia, and anti-convulsant activity. A variety of benzodiazepine-like effects have been observed in vivo and in vitro and have been classified as full agonistic effects (i.e., faithfully mimicking agents such as diazepam with relatively low fractional occupancy of binding sites) or partial agonistic effects (i.e., producing less intense maximal effects and/or requiring relatively high fractional occupancy compared to agents such as diazepam).

[0049] Examples of benzodiazepines that can be used in the present invention include, but are not limited to, alprazolam, brotizolam, chlordiazepoxide, clobazam, clonazepam, clorazepate, demoxepam, diazepam, estazolam, flumazenil, flurazepam, halazepam, lorazepam, midazolam, nitrazepam, nordazepam, oxazepam, prazepam, quazepam, temazepam and triazolam (Goodman & Gilman, *The Pharmacological Basis of Therapeutics*, 9th Ed. McGraw-Hill, 1996, Chapter 17, p363, Table 17-1).

[0050] XANAX® tablets contain alprazolam which is a triazolo analog of the 1,4 benzodiazepine class of central nervous system-active compounds (Physician's Desk Reference® 52 Edition 1998, page 2294). The chemical name of alprazolam is 8-Chloro-1-methyl-6-phenyl-4H-s-triazolo [4,3- α] [1,4] benzodiazepine. XANAX Tablets (alprazolam) are indicated for the management of anxiety disorder (a condition corresponding most closely to the APA Diagnostic and Statistical Manual [DSM-III-R] diagnosis of generalized anxiety disorder) or the short-term relief of symptoms of anxiety.

[0051] LIBRIUM® (chlordiazepoxide HCl) is 7-chloro-2-(methylamino)-5-phenyl-3H-1,4-benzodiazepine 4-oxide hydrochloride (Physician's Desk Reference® 52 Edition 1998, page 2522). Librium is indicated for the management of anxiety disorders or for the short-term relief of symptoms of anxiety, withdrawal symptoms of acute alcoholism, and preoperative apprehension and anxiety.

[0052] KLONOPIN® (clonazepam) is 5-(2-chlorophenyl)-1,3-dihydro-7-nitro-2H-1,4-benzodiazepin-2-one (Physician's Desk Reference® 52 Edition 1998, page 2475). Klonopin is useful alone or as an adjunct in the treatment of the Lennox-Gastaut syndrome (petit mal variant), akinetic and myoclonic seizures. Klonopin is also indicated for the treatment of panic disorder, with or without agoraphobia, as defined in DSM-IV.

[0053] TRANXENE® (clorazepate dipotassium) is indicated for the management of anxiety disorders or for the short-term relief of the symptoms of anxiety, as adjunctive therapy in the management of partial seizures, and for the symptomatic relief of acute alcohol withdrawal (Physician's Desk Reference® 52 Edition 1998, pages 472-473).

[0054] VALIUM® (diazepam) is a benzodiazepine derivative. Chemically, diazepam is 7-chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one (Physician's Desk Reference® 52 Edition 1998, page 2527). Valium is indicated for the management of anxiety disorders or for the short-term relief of the symptoms of anxiety.

[0055] PROSOM™ (estazolam tablets) is 8-chloro-6-phenyl-4H-s-triazolo[4,3- α] [1,4] benzodiazepine (Physician's Desk Reference® 52 Edition 1998, pages 470-471). ProSom (estazolam) is indicated for the short-term management of insomnia characterized by difficulty in falling asleep, frequent nocturnal awakenings, and/or early morning awakenings.

[0056] ROMAZICON® (flumazenil) is a benzodiazepine receptor antagonist (Physician's Desk Reference® 52 Edition 1998, pages 2494-2495). Chemically, flumazenil is ethyl 8-fluoro-5,6-dihydro-5-methyl-6-oxo-4H-imidazo(1,5-a)(1,4) benzodiazepine-3-carboxylate. ROMAZICON is indicated for the complete or partial reversal of the sedative effects of benzodiazepines in cases where general anesthesia has been induced and/or maintained with benzodiazepines, where sedation has been produced with benzodiazepines for

diagnostic and therapeutic procedures, and for the management of benzodiazepine overdose.

[0057] DALMANE® (flurazepam hydrochloride) is chemically 7-chloro-1-[2-(di-ethylamino)ethyl]-5-(o-fluorophenyl)-1,3-dihydro-2H-1,4-benzodiazepin-2-one dihydrochloride (Physician's Desk Reference® 52 Edition 1998, page 2520). Dalmane is a hypnotic agent useful for the treatment of insomnia characterized by difficulty in falling asleep, frequent nocturnal awakenings, and/or early morning awakenings.

[0058] ATIVAN® (lorazepam) has the chemical formula, 7-chloro-5-(o-chlorophenyl)-1,3-dihydro-3-hydroxy-2H-1,4-benzodiazepin-2-one (Physician's Desk Reference® 52 Edition 1998, page 3013). Ativan (lorazepam) is indicated for the management of anxiety disorders or for the short-term relief of the symptoms of anxiety or anxiety associated with depressive symptoms.

[0059] VERSED® (midazolam HCl) is 8-chloro-6-(2-fluorophenyl)-1-methyl-4H-imidazo[1,5-a][1,4]benzodiazepine (Physician's Desk Reference® 52 Edition 1998, pages 2512-2513).

[0060] SERAX® (oxazepam) is the first of a chemical series of compounds known as the 3-hydroxybenzodiazepinones (Physician's Desk Reference® 52 Edition 1998, page 3132). Serax (oxazepam) is indicated for the management of anxiety disorders or for the short-term relief of the symptoms of anxiety.

[0061] DORAL® (quazepam) is a trifluoroethyl benzodiazepine hypnotic agent, having the chemical name 7-chloro-5-(o-fluoro-phenyl)-1,3-dihydro-1-(2,2,2-trifluoroethyl)-2H-1,4-benzodiazepine-2-thione (Physician's Desk Reference® 52 Edition 1998, page 2958). DORAL is indicated for the treatment of insomnia characterized by difficulty in falling asleep, frequent nocturnal awakenings, and/or early morning awakenings.

[0062] RESTORIL® (temazepam) is a benzodiazepine hypnotic agent. The chemical name is 7-chloro-1,3-dihydro-3-hydroxy-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one (Physician's Desk Reference® 52 Edition 1998, page 1894). RESTORIL® (temazepam) is indicated for the short-term treatment of insomnia (generally 7-10 days).

[0063] HALCION® Tablets contain triazolam, a triazolobenzodiazepine hypnotic agent (Physician's Desk Reference® 52 Edition 1998, pages 2275-2276). HALCION is indicated for the short-term treatment of insomnia (generally 7-10 days).

[0064] Antipsychotic agents are used primarily in the management of patients with psychotic or other serious psychiatric illness marked by agitation and impaired reasoning. These drugs have other properties that possibly are useful clinically, including antiemetic and antihistamine effects and the ability to potentiate analgesics, sedatives, and general anesthetics. Antipsychotic agents can also be used with optically pure R(-) fluoxetine. Tricyclic antipsychotic drugs fall into three subtypes: phenothiazines, thioxanthenes and other heterocyclic compounds.

[0065] Examples of phenothiazines include, but are limited to: THORAZINE® (chlorpromazine), SERENTIL® (mesoridazine besylate), MELLARIL® or MILLAZINE® (thioridazine), TINDAL® (acetophenazine), PERMITIL®

or PROLIXIN® (fluphenazine) TRILAFON® (perphenazine) and STELAZINE® (trifluoperazine) (Goodman & Gilman, The Pharmacological Basis of Therapeutics, 9th Ed. McGraw-Hill, 1996, Chapter 18, p404, Table 18-1).

[0066] THORAZINE® (chlorpromazine) is 10-(3-dimethylaminopropyl)-2-chlorophenothiazine, a dimethylamine derivative of phenothiazine (Physician's Desk Reference® 52 Edition 1998, pages 2870-2871). THORAZINE® (chlorpromazine) is indicated, inter alia, for the management of manifestations of psychotic disorders.

[0067] SERENTIL® (mesoridazine besylate) is 10-[2(1-methyl-2-piperidyl)ethyl]-2-methyl-sylfinyl-phenothiazine (Physician's Desk Reference® 52 Edition 1998, pages 725-726). Serentil® (mesoridazine besylate) is indicated in the treatment of, inter alia, emotional withdrawal, conceptual disorganization, anxiety, tension, hallucinatory behavior, suspiciousness and blunted affect in schizophrenic patients.

[0068] TRILAFON® (perphenazine) is (4-[3-(2-chlorophenothiazin-10-yl)propyl-1-piperazineethanol] (Physician's Desk Reference® 52 Edition 1998, page 2666). TRILAFON® (perphenazine) is indicated for use in the management of the manifestations of psychotic disorders and for the control of severe nausea and vomiting in adults.

[0069] STELAZINE® (trifluoperazine) is indicated for the management of the manifestations of psychotic disorders and for the short-term treatment of generalized non-psychotic anxiety (Physician's Desk Reference® 52 Edition 1998, page 2862).

[0070] Examples of thioxanthenes include, but are limited to: TARACTAN® (chlorprothixene) and NAVANE® (thiothixene) (Goodman & Gilman, The Pharmacological Basis of Therapeutics, 9th Ed. McGraw-Hill, 1996, Chapter 18, p404, Table 18-1).

[0071] NAVANE® (thiothixene) is the cis isomer of N,N-dimethyl-9-[3-(4-methyl-1-piperazinyl)-propylidene]thioxanthene-2-sulfonamide (Physician's Desk Reference® 52 Edition 1998, page 2192). NAVANE® (thiothixene) is indicated in the management of manifestations of psychotic disorders.

[0072] Examples of the other heterocyclic compounds that can be used in combination with R(-) fluoxetine include, but are limited to: CLOZARIL® (clozapine), HALDOL® (haloperidol), LOXITANE® (loxapine), MOBAN® (molindone), ORAP® (Pimozide), RISPERDAL® (risperidone), 9-hydroxy-risperidone and NORPRAMIN® (desipramine hydrochloride) (Goodman & Gilman, The Pharmacological Basis of Therapeutics, 9th Ed. McGraw-Hill, 1996, Chapter 18, p404, Table 18-1).

[0073] CLOZARIL® (clozapine) is a tricyclic dibenzodiazepine derivative, 8-chloro-11-(4-methyl-1-piperazinyl)-5H-dibenzo[b,e][1,4]diazepine (Physician's Desk Reference® 52 Edition 1998, page 1834). CLOZARIL® (clozapine) is indicated for the management of severely ill schizophrenic patients who fail to respond adequately to standard antipsychotic drug treatment.

[0074] HALDOL® (haloperidol) is 4-[4-(p-chlorophenyl)-4-hydroxy-piperidone]-4'-fluorobutyrophenone (Physician's Desk Reference® 52 Edition 1998, pages 1997-1998). HALDOL® (haloperidol) is indicated, inter alia, for use in the management of manifestations of psychotic dis-

orders, for the control of tics and vocal utterances of Tourette's Disorder in children and adults, for the treatment of severe behavior problems in children of combative.

[0075] LOXITANE® (loxapine) is 2-Chloro-11-(4-methyl-1-piperazinyl)dibenz[b,f][1,4]oxaxepine (Physician's Desk Reference® 52 Edition 1998, page 1396). LOXITANE® (loxapine) is indicated for the management of the manifestations of psychotic disorders.

[0076] MOBAN® (molindone) is 3-ethyl-6,7-dihydro-2-methyl-5(morpholinomethyl) indol-4(5H)-one hydrochloride (Physician's Desk Reference® 52 Edition 1998, pages 976-977). MOBAN® (molindone) is indicated for the management of the manifestations of psychotic disorders.

[0077] ORAP® (Pimozide) is 1-[1-[4,4-bis(4-fluorophenyl)butyl]4-piperidinyl]-1,3-dihydro-2H-benzimidazole-2-one (Physician's Desk Reference® 52 Edition 1998, page 978). ORAP® (Pimozide) is indicated for the suppression of motor and phonic tics in patients with Tardieu's Disorder who have failed to respond satisfactorily to standard treatment.

[0078] RISPERDAL® (risperidone) is 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one (Physician's Desk Reference® 52 Edition 1998, pages 1309-1310). RISPERDAL® (risperidone) is indicated for the management of the manifestations of psychotic disorders. 9-hydroxy-risperidone is a major active metabolite of risperidone (Id.). This major metabolite has been reported to be approximately equieffective as risperidone in Lacombe, *Can. J. Psychiatry*, 38 (Suppl.):S80-S88 (1993). 9-hydroxy-risperidone can be prepared from risperidone or from other well known starting materials using synthetic techniques well known in the art.

[0079] NORPRAMIN® (desipramine hydrochloride) is 5-H-Dibenz[b,f]azepine-5-propanamine, 10, 11- dihydro-N-methyl-, monohydrochloride (Physician's Desk Reference® 52 Edition 1998, page 1227). NORPRAMIN® (desipramine hydrochloride) is indicated for the treatment of depression.

[0080] Examples of 5-HT_{1A} receptor antagonists and/or 5-HT_{2A} antagonists that can be used with R(-) fluoxetine in accordance with this invention include, but are limited to, alprenolol, WAY 100135, spiperone, VISKEN™ (pindolol), (S)-UH-301, LEVATOL™ (penbutolol), INDERAL™ (propranolol) and tertatolol.

[0081] Alprenolol (1-(1-methylethyl)amino-3-[2-(2-propenyl)phenoxy]-2-propanol) was disclosed by Brandstrom et al., U.S. Pat. No. 3,466,325, which shows its preparation.

[0082] WAY 100135 (N-(t-butyl)-3-[4-(2-methoxyphenyl)piperazin-1-yl]-2-phenylpropanamide) was disclosed by Abou-Gharbia et al., U.S. Pat. No. 4,988,814, which disclosed that the compound has affinity for the 5-HT_{1A} receptor. Cliffe et al., *J. Med. Chem.*, 36:1509-10 (1993) showed that the compound is a 5-HT_{1A} antagonist.

[0083] Spiperone (8-[4-(4-fluorophenyl)-4-oxobutyl]-1-phenyl-1,3,8-triazaspiro[4,5]decan-4-one) is a well-known compound, taught in U.S. Pat. 3,155,669 and 3,155,670. Its activity as a 5-HT_{1A} antagonist is shown by Middlmiss et al., *Neurosci. and Biobehav. Rev.*, 16:75-82, (1992).

[0084] Pindolol (4-(2-hydroxy-3-isopropylaminopropoxy)-indole) was disclosed by Troxler et al., U.S. Pat.

3,471,515, which describes this compound as well as a beta-blocker. Dreshfield et al., *Neurochem. Res.*, 21(5):557-562 (1996) disclosed that S(-) pindolol is a 5-HT_{1A} antagonist. VISKE™ (pindolol) is indicated in the management of hypertension (Physician's Desk Reference® 51 Edition 1997, page 2429). As used in the present application, the term "pindolol" refers to any acid addition salt or the free base, and includes either the racemic mixture or either of the R and S enantiomers.

[0085] (S)-UH-301 ((S)-5-fluoro-8-hydroxy-2-dipropylaminotetralin) is well known to pharmacologists and pharmaceutical chemists. Hillyer et al. taught its synthesis in *J. Med. Chem.*, 33:1541-44 (1990) and Moreau et al., *Brain Res. Bull.*, 29:901-04 (1992) provided considerable in vivo data about the compound.

[0086] Penbutolol (1-(t-butylamino)-2-hydroxy-3-(2-cyclopentylphenoxy)propane) was taught by Ruschig et al., U.S. Pat. No. 3,551,493, which describes it as a beta-blocker. Both the (-) and the (+) enantiomers of penbutolol are of interest; the (-) enantiomer is preferred for the present purpose but both enantiomers and the racemic mixture are included in the word "penbutolol" in this document. LEVATOL™ (penbutolol) is indicated in the management of hypertension (Physician's Desk Reference® 51 Edition 1997, page 2547).

[0087] Propranolol (1-isopropylamino-3-(1-naphthalenyl)-2-propanol) was disclosed by Crowther et al., U.S. Pat. No. 3,337,628 to be a beta-blocker like tertatolol. INDERAL® (propranolol) is indicated in the management of hypertension. INDERAL® (propranolol) is also indicated in the management of myocardial infarction, migraine, essential tremor, hypertrophic subaortic stenosis and pheochromocytoma (Physician's Desk Reference® 51 Edition 1997, pages 2833-2834).

[0088] Tertatolol (8-(3-t-butylamino-2-hydroxypropyl)-thiochroman) was disclosed by Malen et al., U.S. Pat. No. 3,960,891, which teaches it to be a blocker of cardiac beta-adrenergic receptors. Its other activities, including the presently used 5-HT_{1A} antagonist activity, have been discovered since the original patents appeared.

[0089] Examples of non-benzodiazepine and non-tricyclic agents that can be used in this invention include, but are limited to: ZYPREXA™ (olanzapine), BUSPAR® (buspirone hydrochloride), ATARAX® (hydroxyzine hydrochloride), tomoxetine, SEROQUEL® (quetiapine), sertindole and ziprasidone.

[0090] ZYPREXA™ (olanzapine) is 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5]benzodiazepine (Physician's Desk Reference® 52 Edition 1998, page 1512). ZYPREXA™ (olanzapine) is indicated for the management of the manifestations of psychotic disorders.

[0091] BUSPAR® (buspirone hydrochloride) is an anti-anxiety agent that is not chemically or pharmacologically related to the benzodiazepines, barbiturates, or other sedative/anxiolytic drugs (Physician's Desk Reference® 52 Edition 1998, page 782). Chemically, buspirone hydrochloride is 8-[4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl]-8-azaspiro[4,5]decan-7,9-dione monohydrochloride. BUSPAR® (buspirone hydrochloride) is indicated for the treatment of Generalized Anxiety Disorder (ADA).

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[0092] ATARAX® (hydroxyzine hydrochloride) is designated chemically as 1-(p-chlorobenzhydryl)-4[2-(2-hydroxyethoxy)-ethyl] piperazine dihydrochloride (Physician's Desk Reference® 52 Edition 1998, page 2164). ATARAX® (hydroxyzine hydrochloride) is indicated for symptomatic relief of anxiety and tension associated with psychoneurosis, as an adjunct in organic disease states in which anxiety is manifested, in the management of pruritus due to allergic conditions, and as sedative when used as premedication and following general anesthesia.

[0093] SEROQUEL® (Zeneca Pharmaceuticals) (quetiapine) has recently approved by the FDA to manage the manifestations of psychotic disorders (Medical Sciences Bulletin, Issue No. 241 (1997)). Although the exact mechanism of quetiapine is unknown, it is generally believed that the antipsychotic action of quetiapine is largely due to antagonism at the dopamine and serotonin receptors (Arvanitis, et al., *Biol. Psychiatry*, 15:233-246 (1997); Faustman et al., *J. Clin. Psychopharmacol.*, 16:464-466 (1996); Fleischhacker et al., *Drugs*, 53:915-929 (1997); Small et al., *Arch. Gen. Psychiatry*, 54:549-557 (1997)).

[0094] Sertindole is designated chemically as 1-[2-[4-[5-Chloro-1-(4-fluorophenyl)-1H-indol-3-yl]-1-piperidinyl]ethyl]-2-imidazolidinone (*The Merck Index*, 12th Ed., Merck & Co., Inc., Whitehouse Station, N.J., 1996, page 1455). Sertindole can be prepared according to the procedures disclosed in U.S. Pat. No. 4,710,500, the content of which is incorporated herein by reference. Sertindole is a new atypical antipsychotic agent for the treatment of schizophrenia (Brown, et al., *Pharmacotherapy*, 18(1):69-83 (1998)).

[0095] Ziprasidone is designated chemically as 5-[2-[4-(1,2-Benzisothiazol-yl)-1-piperazinyl]ethyl]-6-chloro-1,3-dihydro-2H-indol-2-one (*The Merck Index*, 12th Ed., Merck & Co., Inc., Whitehouse Station, N.J., 1996, page 1737). Ziprasidone can be prepared according to the procedures disclosed in U.S. Pat. No. 4,831,031, the content of which is incorporated herein by reference. Ziprasidone is a novel antipsychotic agent that is in late clinical trials. It has shown antipsychotic efficacy in patients with schizophrenia and schizo-affective disorder and anxiolytic efficacy in patients about to undergo dental surgery (Davis and Markham, *CNS Drugs*, 8(2):153-159 (1997)).

[0096] While all combinations of R(-) fluoxetine and one or more above described biologically active compounds are useful and valuable, certain combinations are particularly valued and are preferred, as follows:

- [0097] R(-) fluoxetine/alprazolam
- [0098] R(-) fluoxetine/brotizolam
- [0099] R(-) fluoxetine/chlordiazepoxide
- [0100] R(-) fluoxetine/clobazam
- [0101] R(-) fluoxetine/clonazepam
- [0102] R(-) fluoxetine/clorazepate
- [0103] R(-) fluoxetine/demoxepam
- [0104] R(-) fluoxetine/diazepam
- [0105] R(-) fluoxetine/estazolam
- [0106] R(-) fluoxetine/flumazenil

- [0107] R(-) fluoxetine/flurazepam
- [0108] R(-) fluoxetine/halazepam
- [0109] R(-) fluoxetine/lorazepam
- [0110] R(-) fluoxetine/midazolam
- [0111] R(-) fluoxetine/nitrazepam
- [0112] R(-) fluoxetine/nordazepam
- [0113] R(-) fluoxetine/oxazepam
- [0114] R(-) fluoxetine/prazepam
- [0115] R(-) fluoxetine/quazepam
- [0116] R(-) fluoxetine/temazepam
- [0117] R(-) fluoxetine/triazolam
- [0118] R(-) fluoxetine/chlorpromazine
- [0119] R(-) fluoxetine/mesoridazine
- [0120] R(-) fluoxetine/thioridazine
- [0121] R(-) fluoxetine/acetophenazine
- [0122] R(-) fluoxetine/fluphenazine
- [0123] R(-) fluoxetine/perphenazine
- [0124] R(-) fluoxetine/trifluoperazine
- [0125] R(-) fluoxetine/chlorprothixene
- [0126] R(-) fluoxetine/thiothixene
- [0127] R(-) fluoxetine/clozapine
- [0128] R(-) fluoxetine/haloperidol
- [0129] R(-) fluoxetine/lloxapine
- [0130] R(-) fluoxetine/molindone
- [0131] R(-) fluoxetine/pimozide
- [0132] R(-) fluoxetine/risperidone
- [0133] R(-) fluoxetine/9-hydroxy-risperidone
- [0134] R(-) fluoxetine/alprenolol
- [0135] R(-) fluoxetine/WAY 100135
- [0136] R(-) fluoxetine/spiperone
- [0137] R(-) fluoxetine/S(-) pindolol
- [0138] R(-) fluoxetine/R(+) pindolol
- [0139] R(-) fluoxetine/racemic pindolol
- [0140] R(-) fluoxetine/(S)-UH-301
- [0141] R(-) fluoxetine/penbutolol
- [0142] R(-) fluoxetine/propranolol
- [0143] R(-) fluoxetine/tertanolol
- [0144] R(-) fluoxetine/desipramine
- [0145] R(-) fluoxetine/clonidine
- [0146] R(-) fluoxetine/olanzapine
- [0147] R(-) fluoxetine/methylphenidate
- [0148] R(-) fluoxetine/buspirone
- [0149] R(-) fluoxetine/hydroxyzine

[0150] R(-) fluoxetine/tomoxetine

[0151] R(-) fluoxetine/quetiapine

[0152] R(-) fluoxetine/sertindole

[0153] R(-) fluoxetine/ziprasidone

[0154] The magnitude of a prophylactic or therapeutic dose of R(-) fluoxetine, of course, vary with the nature of the severity of the condition to be treated and its route of administration. It will also vary according to the age, weight and response of the individual patient. In general the daily dose range of R(-) fluoxetine in treatment of diseases or disorders, especially psychotic or psychiatric diseases or disorders lie within the range from about 1 mg to about 100 mg per day, preferably about 5 mg to about 60 mg per day, and most preferably from about 10 mg to about 40 mg per day, in single or divided doses. Effective amounts of the therapeutic agents to be used in combination with R(-) fluoxetine are based on the recommended doses known to those skilled in the art for the various diseases or disorders. It should be noted that the attending physician would know how to and when to terminate, interrupt, or adjust therapy to lower dosage due to toxicity, bone marrow, liver or kidney dysfunctions or adverse drug-drug interaction. Conversely, the attending physician would also know to adjust treatment to higher levels if the clinical response is not adequate (precluding toxicity).

[0155] A therapeutically effective dose refers to that amount of the compound sufficient to result in amelioration of symptoms or a prolongation of survival in a patient. As used herein, the term "an effective amount" and the term "a therapeutically effective dose/amount" has the same meaning. Toxicity and therapeutic efficacy of such compounds can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, e.g., for determining the LD50 (the dose lethal to 50% of the population) and the ED50 (the dose therapeutically effective in 50% of the population). The dose ratio between toxic and therapeutic effects is the therapeutic index and it can be expressed as the ratio LD50/ED50. Compounds which exhibit large therapeutic indices are preferred. The data obtained from these cell culture assays and animal studies can be used in formulating a range of dosage for use in humans. The dosage of such compounds lies preferably within a range of circulating concentrations that include the ED50 with little or no toxicity. The dosage may vary within this range depending upon the dosage form employed and the route of administration utilized. For any compound used in the method of the invention, the therapeutically effective dose can be estimated initially from cell culture assays. A dose may be formulated in animal models to achieve a circulating plasma concentration range that includes the IC50 i.e., the concentration of the test compound which achieves a half-maximal inhibition of its target from infected cells compared to untreated control as determined in cell culture. Such information can be used to more accurately determine useful doses in humans.

[0156] In a certain embodiment of the invention, that is, a method of treating or preventing a psychotic or psychiatric disease or disorder, such as depression, an effective amount of R(-) fluoxetine and an effective amount of a biologically active 5-HT_{1A} receptor antagonist is administered for a first period of time; and then an effective amount of R(-)

fluoxetine and a reduced amount of said biologically active 5-HT_{1A} receptor antagonist is administered for a second period of time. Preferably, 5-HT_{1A} receptor antagonist used herein is pindolol. Also preferably, the first period of time is from about 2 to about 6 weeks and the second period of time is from about 2 to about 20 days. A kit which comprises a plurality of dosage forms each comprising an effective amount of R(-) fluoxetine and a plurality of dosage forms each comprising an effective amount of a biologically active 5-HT_{1A} receptor antagonist, and a plurality of dosage forms each comprising a reduced amount of said biologically active 5-HT_{1A} receptor antagonist can be used in the above method. A kit which comprises a single unit dosage form of an effective amount of R(-) fluoxetine, a single unit dosage form of an effective amount of a biologically active 5-HT_{1A} receptor antagonist, and a single unit dosage form of a reduced amount of said biologically active 5-HT_{1A} receptor antagonist can also be used in the above method.

[0157] Any suitable route of administration may be employed for providing the patient with an effective dosage of the pharmaceutical compositions of the present invention. For example, oral, rectal, parenteral, transdermal, sublingual subcutaneous, intramuscular, inhalation and the like may be employed. Dosage forms include tablets, troches, dispersions, suspensions, solutions, capsules, patches and the like.

[0158] The pharmaceutical compositions of the present invention comprise R(-) fluoxetine and other active ingredients or a pharmaceutically acceptable salt thereof, and may also contain a pharmaceutically acceptable carrier and optionally other therapeutic ingredients. The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic acids including inorganic acids and organic acids.

[0159] Since R(-) fluoxetine, one of the key component of the pharmaceutical composition of the present invention, is basic, salts may be prepared from pharmaceutically acceptable nontoxic acids, including inorganic and organic acids. Such acids include acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethenesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pantoic, pantothenic, phosphoric, succinic, sulfuric, tartaric acid, p-toluenesulfonic and the like. Particularly preferred are hydrobromic, hydrochloric, phosphoric and sulfuric acids.

[0160] The compositions include compositions suitable for oral, rectal, parenteral (including subcutaneous, intramuscular, and intravenous), although the most suitable route in any given case will depend on the nature and severity of the condition being treated. The most preferred route of the present invention is oral. They may be conveniently presented in unit dosage form and prepared by any of the methods well-known in the art of pharmacy.

[0161] The pharmaceutical carrier, which is included in the pharmaceutical compositions of the present invention, may take a wide variety of forms depending on the form of preparation desired for administration, e.g., oral or parenteral (including intravenous). In preparing the compositions for oral dosage form, any of the usual pharmaceutical media may be employed, such as, for example, water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents and the like in the case of oral liquid prepara-

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tions, such as, for example, suspensions, elixir and solutions; or carriers such as starches, sugars, microcrystalline cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents and the like in the case of oral solid preparations such as, for example, powders, capsules and tablets, with the solid oral preparations being preferred over the liquid preparations. The most preferred solid oral preparation is capsules. Because of their ease of administration, tablets and capsules represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are obviously employed. If desired, tablets may be coated by standard aqueous or nonaqueous techniques.

[0162] In addition to the common dosage forms set out above, the pharmaceutical compositions of the present invention may also be administered by controlled release means and/or delivery devices such as those described in U.S. Pat. Nos. 3,536,809; 3,598,123; 3,630,200; 3,845,770; 3,847,770; 3,916,899; 4,008,719; 4,687,610; 4,769,027; 5,059,595; 5,073,543; 5,120,548; 5,354,566; 5,591,767; 5,639,476; 5,674,533 and 5,733,566, the disclosures of which are hereby incorporated by reference. The use of a racemic mixture of fluoxetine in a sustained release formulation is disclosed and/or claimed in U.S. Pat. Nos. 4,797,286 and 4,947,092.

[0163] Pharmaceutical compositions of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient, as a powder or granules or as a solution or a suspension in an aqueous liquid, a non-aqueous liquid, an oil-in-water emulsion or a water-in-oil liquid emulsion. Such compositions may be prepared by any of the methods of pharmacy but all methods include the step of bringing into association the active ingredient with the carrier which constitutes one or more necessary ingredients. In general, the compositions are prepared by uniformly and intimately admixing the active ingredient with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product into the desired presentation. For example, a tablet may be prepared by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine, the active ingredient in a free-flowing form such as powder or granules, optionally mixed with a binder, lubricant, inert diluent, surface active or dispersing agent. Molded tablets may be made by molding in a suitable machine, a mixture of the powdered compound moistened with an inert liquid diluent.

[0164] The present invention is not to be limited in scope by the specific embodiments described herein. Indeed, various modifications of the invention in addition to those described herein will become apparent to those skilled in the art from the foregoing description. Such modifications are intended to fall within the scope of the appended claims.

[0165] Various references are cited herein, the disclosures of which are incorporated by reference in their entireties.

What is claimed is:

1. A pharmaceutical composition which comprises an effective amount of R(-) fluoxetine or a pharmaceutically acceptable salt thereof, substantially free of its S(+) stereoisomer, an effective amount of a biologically active benzodiazepine and a pharmaceutically acceptable carrier.

2. The pharmaceutical composition of claim 1, wherein said biologically active benzodiazepine is selected from the group consisting of alprazolam, brotizolam, chlordiazepoxide, clobazam, clonazepam, clorazepate, demoxepam, diazepam, estazolam, flumazenil, flurazepam, halazepam, lorazepam, midazolam, nitrazepam, nordazepam, oxazepam, prazepam, quazepam, temazepam and triazolam.

3. The pharmaceutical composition of claim 1, wherein the amount of R(-) fluoxetine is from about 5 mg to about 100 mg.

4. The pharmaceutical composition of claim 1, wherein the R(-) fluoxetine is present in an amount on weight basis, relative to S(+) fluoxetine, from about 100:1 to about 10,000:1.

5. The pharmaceutical composition of claim 1, wherein the pharmaceutically acceptable salt of R(-) fluoxetine is R(-) fluoxetine hydrochloride.

6. A pharmaceutical composition which comprises an effective amount of R(-) fluoxetine or a pharmaceutically acceptable salt thereof, substantially free of its S(+) stereoisomer, an effective amount of a biologically active tricyclic antipsychotic compound and a pharmaceutically acceptable carrier.

7. The pharmaceutical composition of claim 6, wherein said biologically active tricyclic antipsychotic compound is selected from the group consisting of chlorpromazine, mesoridazine, thioridazine, acetophenazine, fluphenazine, perphenazine, trifluoperazine, chlorprothixene, thiothixene, clozapine, haloperidol, loxapine, molindone, pimozide, risperidone, 9-hydroxy-risperidone and desipramine.

8. The pharmaceutical composition of claim 6, wherein the amount of the R(-) fluoxetine is from about 5 mg to about 100 mg.

9. The pharmaceutical composition of claim 6, wherein the R(-) fluoxetine is present in an amount on weight basis, relative to S(+) fluoxetine, from about 100:1 to about 10,000:1.

10. The pharmaceutical composition of claim 6, wherein the pharmaceutically acceptable salt of R(-) fluoxetine is R(-) fluoxetine hydrochloride.

11. A pharmaceutical composition which comprises an effective amount of R(-) fluoxetine or a pharmaceutically acceptable salt thereof, substantially free of its S(+) stereoisomer, an effective amount of a biologically active 5-HT_{1A} receptor antagonist and a pharmaceutically acceptable carrier.

12. The pharmaceutical composition of claim 11, wherein said biologically active 5-HT_{1A} receptor antagonist is selected from the group consisting of alprenolol, WAY 100135, spiperone, pindolol, (S)-UH-301, penbutolol, propranolol and tertatolol.

13. The pharmaceutical composition of claim 11, wherein the amount of R(-) fluoxetine is from about 5 mg to about 100 mg.

14. The pharmaceutical composition of claim 11, wherein the R(-) fluoxetine is present in an amount on weight basis, relative to S(+) fluoxetine, from about 100:1 to about 10,000:1.

15. The pharmaceutical composition of claim 11, wherein the pharmaceutically acceptable salt of R(-) fluoxetine is R(-) fluoxetine hydrochloride.

16. A pharmaceutical composition which comprises an effective amount of R(-) fluoxetine or a pharmaceutically acceptable salt thereof, substantially free of its S(+) stereoisomer.

oisomer, an effective amount of a biologically active compound selected from the group consisting of buspirone, hydroxyzine, lorazepam, olanzapine, quetiapine, risperidone, 9-hydroxy-risperidone, sertindole, tomozetone, valium and ziprasidone and a pharmaceutically acceptable carrier.

17. The pharmaceutical composition of claim 16, wherein the amount of R(-) fluoxetine is from about 5 mg to about 100 mg.

18. The pharmaceutical composition of claim 16, wherein the R(-) fluoxetine is present in an amount on weight basis, relative to S(+) fluoxetine, from about 100:1 to about 10,000:1.

19. The pharmaceutical composition of claim 16, wherein the pharmaceutically acceptable salt of R(-) fluoxetine is R(-) fluoxetine hydrochloride.

20. A pharmaceutical composition which comprises an effective amount of R(-) fluoxetine or a pharmaceutically acceptable salt thereof, substantially free of its S(+) stereoisomer, an effective amount of a biologically active compound selected from the group consisting of racemic pindolol, S(-) pindolol and R(+) pindolol and a pharmaceutically acceptable carrier.

21. The pharmaceutical composition of claim 20, wherein the amount of R(-) fluoxetine is from about 5 mg to about 100 mg.

22. The pharmaceutical composition of claim 20, wherein the R(-) fluoxetine is present in an amount on weight basis, relative to S(+) fluoxetine, from about 100:1 to about 10,000:1.

23. The pharmaceutical composition of claim 20, wherein the pharmaceutically acceptable salt of R(-) fluoxetine is R(-) fluoxetine hydrochloride.

24. A pharmaceutical composition which comprises an effective amount of R(-) fluoxetine or a pharmaceutically acceptable salt thereof, substantially free of its S(+) stereoisomer, an effective amount of a biologically active 5-HT₃ receptor agonist, and a pharmaceutically acceptable carrier.

25. The pharmaceutical composition of claim 24, wherein the R(-) fluoxetine is present in an amount on weight basis, relative to S(+) fluoxetine, from about 100:1 to about 10,000:1.

26. The pharmaceutical composition of claim 24, wherein the pharmaceutically acceptable salt of R(-) fluoxetine is R(-) fluoxetine hydrochloride.

27. A method of treating or preventing a psychotic or psychiatric disease or disorder in a mammal which comprises administering to said mammal, to which such treatment or prevention is needed, an effective amount of the pharmaceutical composition of claim 1.

28. A method of treating or preventing a psychotic or psychiatric disease or disorder in a mammal which comprises administering to said-mammal, to which such treatment or prevention is needed, an effective amount of the pharmaceutical composition of claim 6.

29. A method of treating or preventing a psychotic or psychiatric disease or disorder in a mammal which comprises administering to said mammal, to which such treatment or prevention is needed, an effective amount of the pharmaceutical composition of claim 11.

30. A method of treating or preventing a psychotic or psychiatric disease or disorder in a mammal which comprises administering to said mammal, to which such treatment or prevention is needed, an effective amount of the pharmaceutical composition of claim 16.

31. A method of treating or preventing a psychotic or psychiatric disease or disorder in a mammal which comprises administering to said mammal, to which such treatment or prevention is needed, an effective amount of the pharmaceutical composition of claim 20.

32. A method of treating or preventing a psychotic or psychiatric disease or disorder in a mammal which comprises administering to said mammal, to which such treatment or prevention is needed, an effective amount of the pharmaceutical composition of claim 24.

33. A method of treating or preventing a disease or disorder in a mammal which comprises administering to said mammal, to which such treatment or prevention is needed, an effective amount of R(-) fluoxetine or a pharmaceutically acceptable salt thereof substantially free of its S(+) stereoisomer, and an effective amount of a biologically active benzodiazepine.

34. The method of claim 33, wherein the psychotic or psychiatric disease or disorder is depression.

35. The method of claim 33, wherein said biologically active benzodiazepine is selected from the group consisting of alprazolam, brotizolam, chlordiazepoxide, clobazam, clonazepam, clorazepate, demoxepam, diazepam, estazolam, flumazenil, flurazepam, halazepam, lorazepam, midazolam, nitrazepam, nordazepam, oxazepam, prazepam, quazepam, temazepam and triazolam.

36. The method of claim 33, wherein the amount of R(-) fluoxetine is from about 5 mg to about 100 mg.

37. The method of claim 33, wherein the R(-) fluoxetine is present in an amount on weight basis, relative to S(+) fluoxetine, from about 100:1 to about 10,000:1.

38. The method of claim 33, wherein the pharmaceutically acceptable salt of R(-) fluoxetine is R(-) fluoxetine hydrochloride.

39. The method of claim 33, wherein said disease or disorder is a psychotic or psychiatric disease or disorder.

40. The method of claim 39, wherein the disease or disorder is selected from the group consisting of anxiety disorder, depression, alcohol withdrawal, preoperative apprehension, Lennox-Gastaut syndrome (petit mal variant), seizures, panic disorder, skeletal muscle spasm, spasticity caused by upper motor neuron disorders, athetosis and stiffman syndrome, convulsive disorders and insomnia.

41. A method of treating or preventing a psychotic or psychiatric disease or disorder in a mammal which comprises administering to said-mammal, to which such treatment or prevention is needed, an effective amount of R(-) fluoxetine or a pharmaceutically acceptable salt thereof, substantially free of its S(+) stereoisomer, and an effective amount of a biologically active tricyclic antipsychotic compound.

42. The method of claim 41, wherein the psychotic or psychiatric disease or disorder is depression.

43. The method of claim 41, wherein said biologically active tricyclic antipsychotic compound is selected from the group consisting of chlorpromazine, mesoridazine, thioridazine, acetophenazine, fluphenazine, perphenazine, trifluoperazine, chlorprothixene, thiothixene, clozapine, haloperidol, loxapine, molindone, pimozide, risperidone, 9-hydroxy-risperidone and desipramine.

44. The method of claim 41, wherein the amount of the R(-) fluoxetine is from about 5 mg to about 100 mg.

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45. The method of claim 41, wherein the R(-) fluoxetine is present in an amount on weight basis, relative to S(+) fluoxetine, from about 100:1 to about 10,000:1.

46. The method of claim 41, wherein the pharmaceutically acceptable salt of R(-) fluoxetine is R(-) fluoxetine hydrochloride.

47. The method of claim 43, wherein the disease or disorder is selected from the group consisting of anxiety disorder, depression, nausea, vomiting, restlessness and apprehension before surgery, acute intermittent porphyria, tetanus, intractable hiccups, severe behavioral problems and hyperactivity in children, emotional withdrawal, conceptual disorganization, tension, hallucinatory behavior, suspiciousness and blunted affect in schizophrenic patients and Tourette's Disorder.

48. A method of treating or preventing a psychotic or psychiatric disease or disorder in a mammal which comprises administering to said mammal, to which such treatment or prevention is needed, an effective amount of R(-) fluoxetine, or a pharmaceutically acceptable salt thereof, substantially free of its S(+) stereoisomer, and an effective amount of a 5-HT_{1A} receptor antagonist.

49. The method of claim 48, wherein the psychotic or psychiatric disease or disorder is depression.

50. The method of claim 48, wherein the amount of R(-) fluoxetine is from about 5 mg to about 100 mg.

51. The method of claim 48, wherein the R(-) fluoxetine is present in an amount on weight basis, relative to S(+) fluoxetine, from about 100:1 to about 10,000:1.

52. The method of claim 48, wherein the pharmaceutically acceptable salt of R(-) fluoxetine is R(-) fluoxetine hydrochloride.

53. A method of treating or preventing a psychotic or psychiatric disease or disorder in a mammal which comprises administering to said mammal, to which such treatment or prevention is needed, an effective amount of R(-) fluoxetine, or a pharmaceutically acceptable salt thereof, substantially free of its S(+) stereoisomer, and an effective amount of a 5-HT₃ receptor agonist.

54. The method of claim 53, wherein the psychotic or psychiatric disease or disorder is depression.

55. The method of claim 53, wherein the amount of R(-) fluoxetine is from about 5 mg to about 100 mg.

56. The method of claim 53, wherein the R(-) fluoxetine is present in an amount on weight basis, relative to S(+) fluoxetine, from about 100:1 to about 10,000:1.

57. The method of claim 53, wherein the pharmaceutically acceptable salt of R(-) fluoxetine is R(-) fluoxetine hydrochloride.

58. A method of treating or preventing post-myocardial infarction depression in a mammal which comprises administering to said mammal, to which such treatment or prevention is needed, an effective amount of R(-) fluoxetine, or a pharmaceutically acceptable salt thereof, substantially free of its S(+) stereoisomer, and an effective amount of a β -adrenergic antagonist.

59. The method of claim 58, wherein the β -adrenergic antagonist is S(-) pindolol.

60. The method of claim 58, wherein the amount of R(-) fluoxetine is from about 5 mg to about 100 mg.

61. The method of claim 58, wherein the R(-) fluoxetine is present in an amount on weight basis, relative to S(+) fluoxetine, from about 100:1 to about 10,000:1.

62. The method of claim 58, wherein the pharmaceutically acceptable salt of R(-) fluoxetine is R(-) fluoxetine hydrochloride.

63. A method of treating or preventing posttraumatic stress disorder in a mammal which comprises administering to said mammal, to which such treatment or prevention is needed, an effective amount of R(-) fluoxetine, or a pharmaceutically acceptable salt thereof, substantially free of its S(+) stereoisomer, and an effective amount of a 5-HT_{1A} receptor antagonist.

64. The method of claim 63, wherein the 5-HT_{1A} receptor antagonist is S(-) pindolol or R(+) pindolol.

65. The method of claim 63, wherein the amount of R(-) fluoxetine is from about 5 mg to about 100 mg.

66. The method of claim 63, wherein the R(-) fluoxetine is present in an amount on weight basis, relative to S(+) fluoxetine, from about 100:1 to about 10,000:1.

67. The method of claim 63, wherein the pharmaceutically acceptable salt of R(-) fluoxetine is R(-) fluoxetine hydrochloride.

68. A method of treating or preventing a psychotic or psychiatric disease or disorder in a mammal which comprises:

a) administering to said mammal an effective amount of R(-) fluoxetine or a pharmaceutically acceptable salt thereof substantially free of its S(+) stereoisomer, and an effective amount of a biologically active 5-HT_{1A} receptor antagonist for a first period of time; and

b) after the first period of time, administering to said mammal an effective amount of R(-) fluoxetine or a pharmaceutically acceptable salt thereof substantially free of its S(+) stereoisomer and a reduced amount of said biologically active 5-HT_{1A} receptor antagonist for a second period of time.

69. The method of claim 68, wherein the psychotic or psychiatric disease or disorder is depression.

70. The method of claim 68, wherein the biologically active 5-HT_{1A} receptor antagonist is S(-) pindolol or R(+) pindolol.

71. The method of claim 68, wherein the amount of R(-) fluoxetine is from about 5 mg to about 100 mg.

72. The method of claim 68, wherein the R(-) fluoxetine is present in an amount on weight basis, relative to S(+) fluoxetine, from about 100:1 to about 10,000:1.

73. The method of claim 68, wherein the pharmaceutically acceptable salt of R(-) fluoxetine is R(-) fluoxetine hydrochloride.

74. The method of claim 68, wherein the first period of time is about 2 to 6 weeks.

75. The method of claim 68, wherein the second period of time is about 5 to 20 days.

76. A kit which comprises:

a) a plurality of dosage forms each comprising an effective amount of R(-) fluoxetine or a pharmaceutically acceptable salt thereof substantially free of its S(+) stereoisomer;

b) a plurality of dosage forms each comprising an effective amount of a biologically active 5-HT_{1A} receptor antagonist; and

c) a plurality of dosage forms each comprising a reduced amount of said biologically active 5-HT_{1A} receptor antagonist.

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77. The kit of claim 76, wherein the biologically active 5-HT_{1A} receptor antagonist is S(-) pindolol or R(+) pindolol.

78. The kit of claim 76, wherein the pharmaceutically acceptable salt of R(-) fluoxetine is R(-) fluoxetine hydrochloride.

79. A method of treating posttraumatic stress disorder in a human which comprises administering to said human, to which such treatment or prevention is needed, an effective amount of R(-) fluoxetine, or a pharmaceutically acceptable salt thereof, substantially free of its S(+) stereoisomer, and an effective amount of a biologically active compound.

80. A method of treating or preventing a disease or disorder in a mammal which comprises administering to said mammal, to which such treatment or prevention is needed, an effective amount of R(-) fluoxetine or a pharmaceutically acceptable salt thereof substantially free of its S(+) stereoisomer, and an effective amount of a compound selected from

the group consisting of quetiapine, sertindole and ziprasidone.

81. The method of claim 80, wherein the disease or disorder is psychotic disease or disorder.

82. The method of claim 81, wherein the psychotic disease or disorder is schizophrenia.

83. The method of claim 80, wherein the amount of R(-) fluoxetine is from about 5 mg to about 100 mg.

84. The method of claim 80, wherein the R(-) fluoxetine is present in an amount on weight basis, relative to S(+) fluoxetine, from about 100:1 to about 10,000:1.

85. The method of claim 80, wherein the pharmaceutically acceptable salt of R(-) fluoxetine is R(-) fluoxetine hydrochloride.

* * * * *



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160(19) **United States**(12) **Patent Application Publication**
Radulovacki et al.(10) **Pub. No.: US 2003/0130266 A1**(43) **Pub. Date: Jul. 10, 2003**(54) **PHARMACOLOGICAL TREATMENT FOR
SLEEP APNEA****Publication Classification**(76) Inventors: **Miodrag Radulovacki**, Chicago, IL
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514/304; 514/252.12; 514/259.41;
514/288(21) Appl. No.: **10/285,277**(57) **ABSTRACT**(22) Filed: **Oct. 31, 2002****Related U.S. Application Data**(63) Continuation-in-part of application No. 10/016,901,
filed on Dec. 14, 2001.

The present invention relates generally to pharmacological methods for the prevention of amelioration of sleep-related breathing disorders via administration of agents or combinations of agents that possess serotonin-related pharmacological activity.

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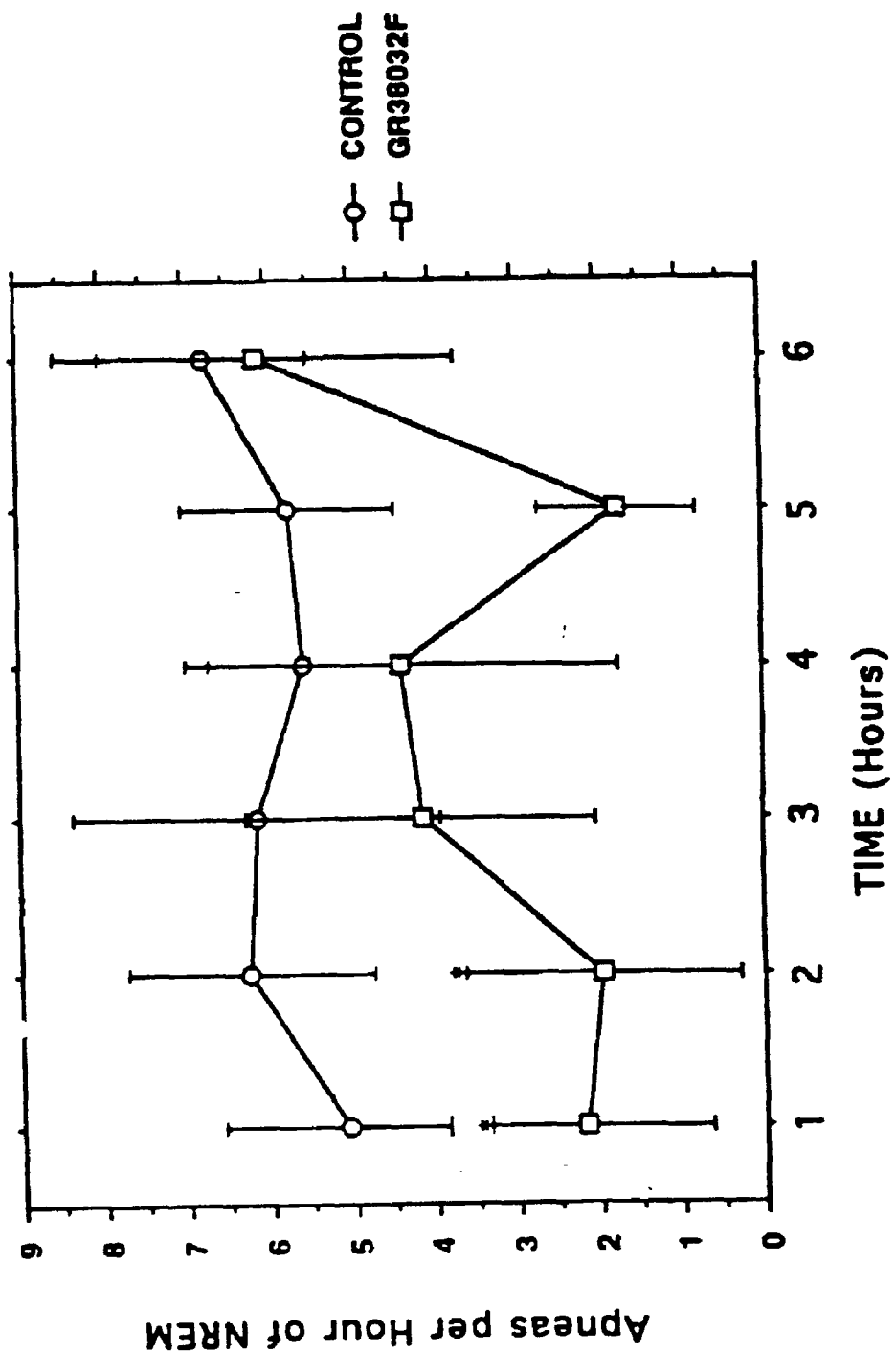


FIGURE 1

74
162

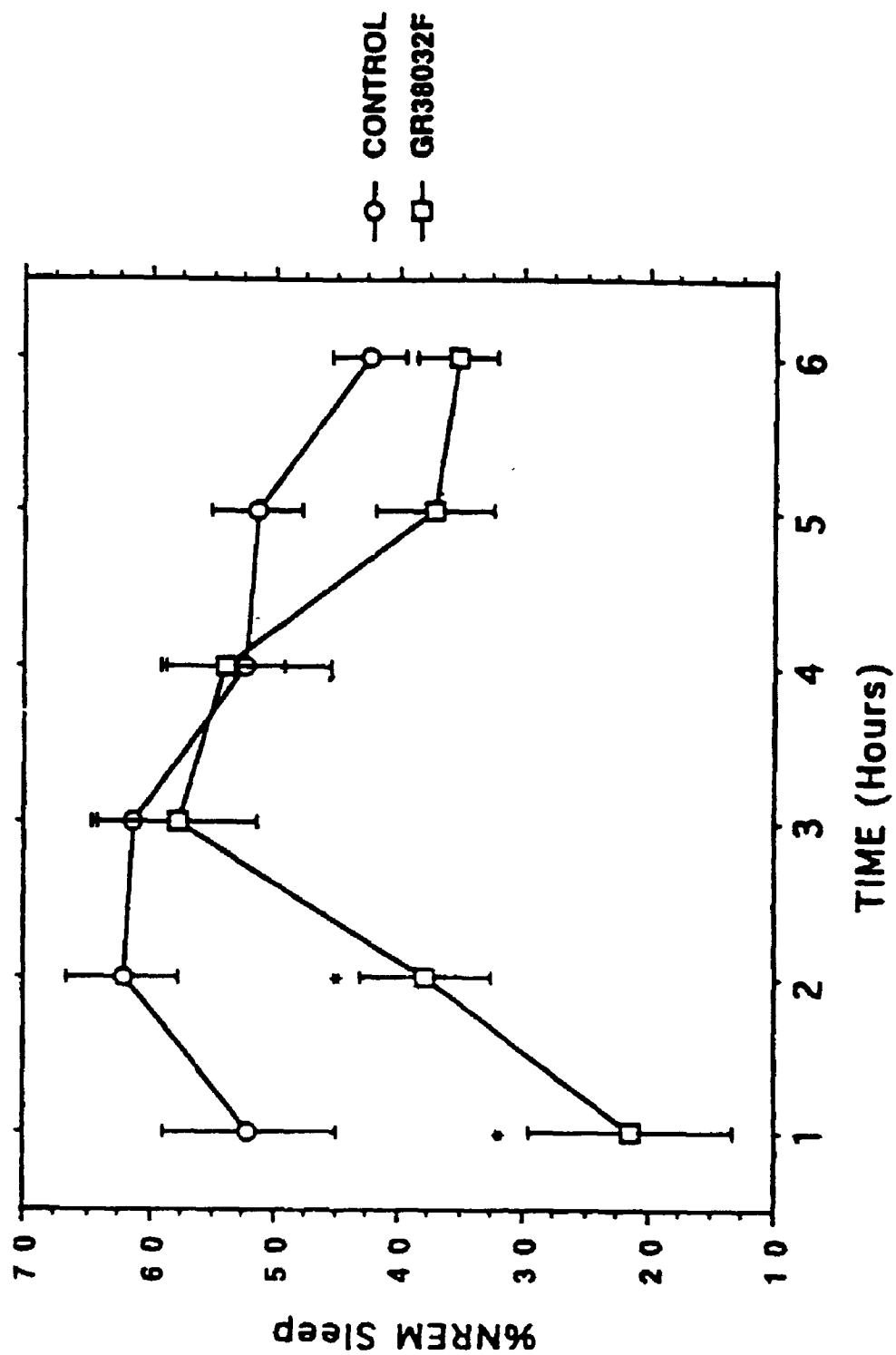


FIGURE 2

75
163

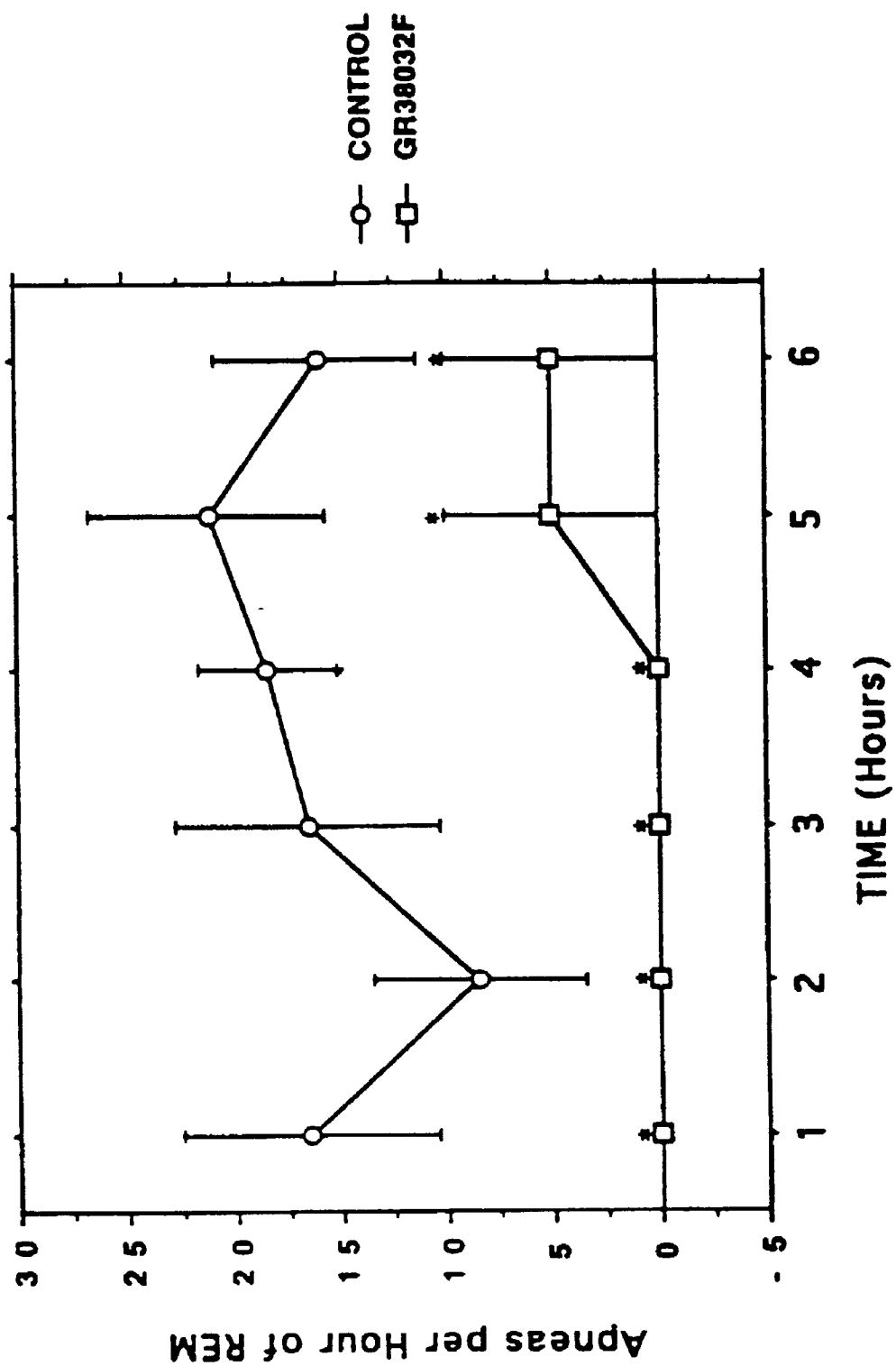


FIGURE 3

76
164

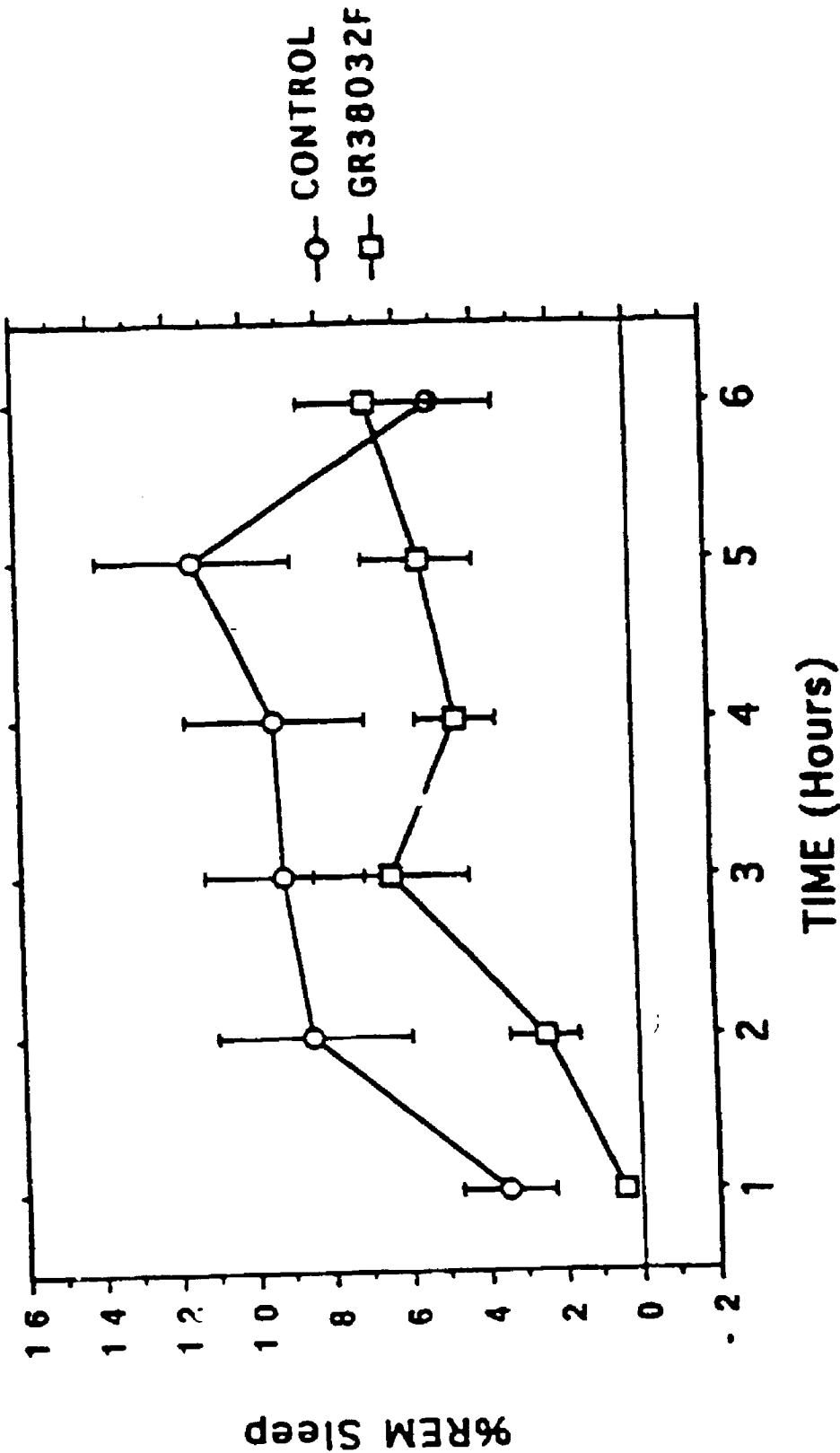


FIGURE 4

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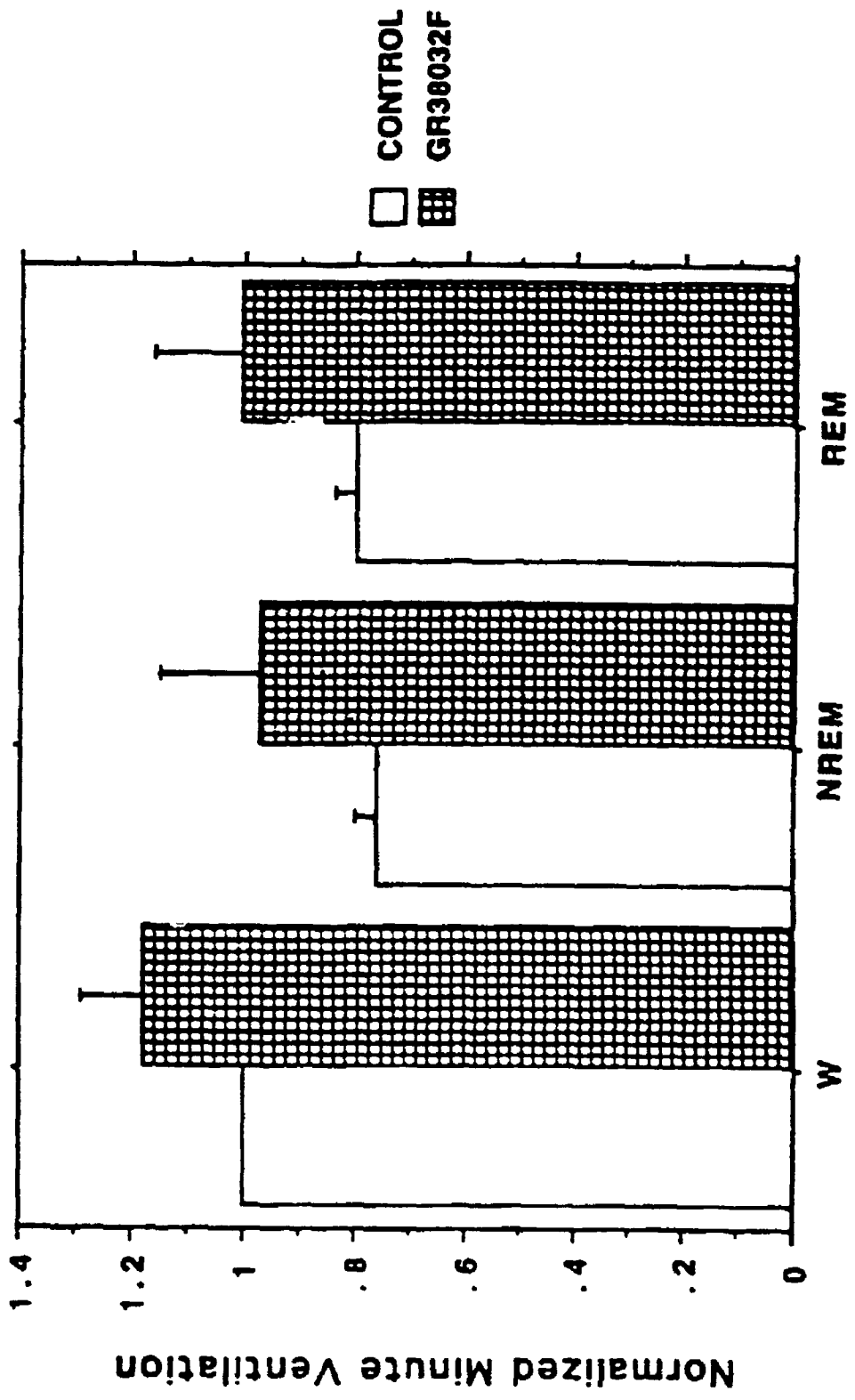


FIGURE 5

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166

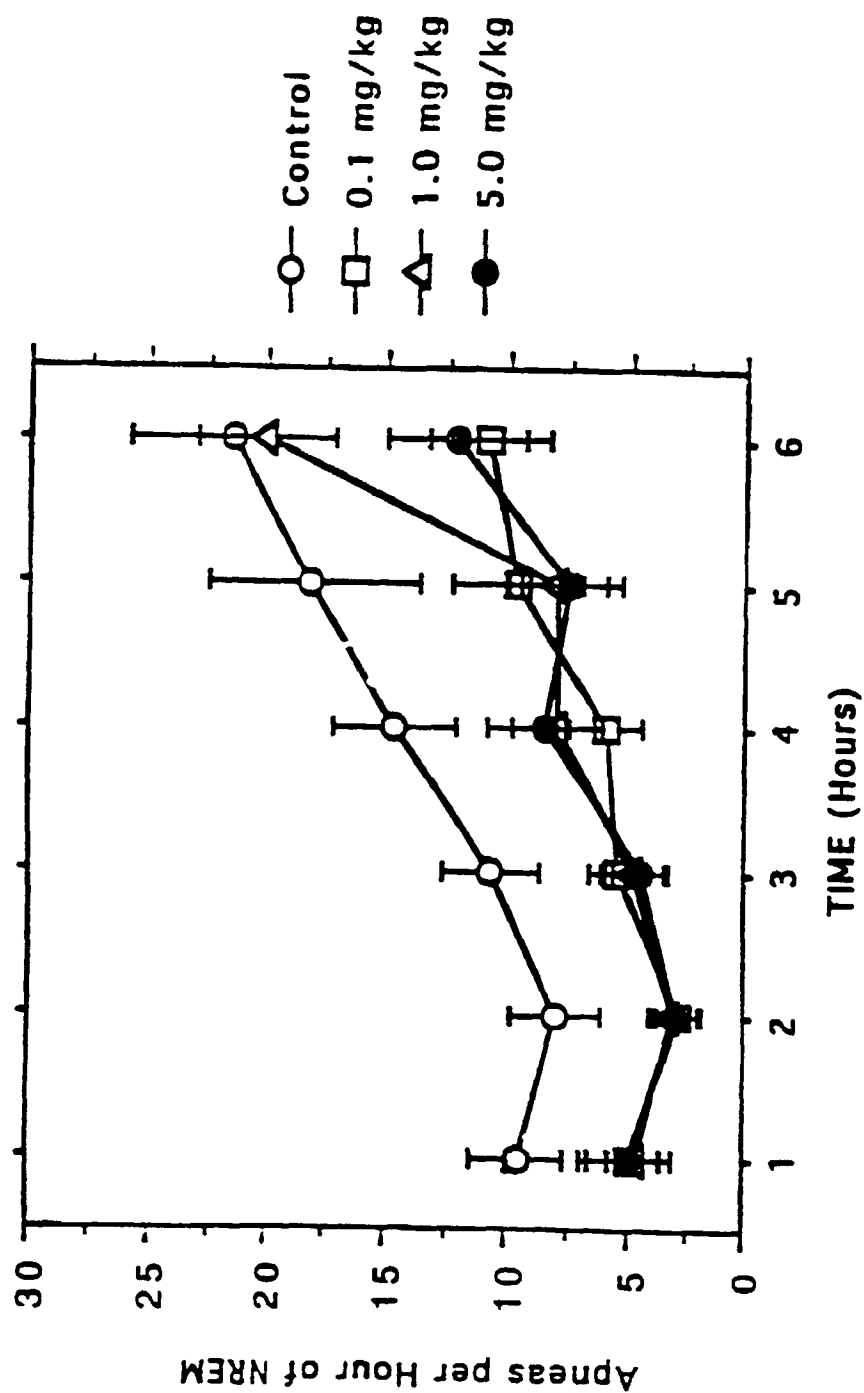
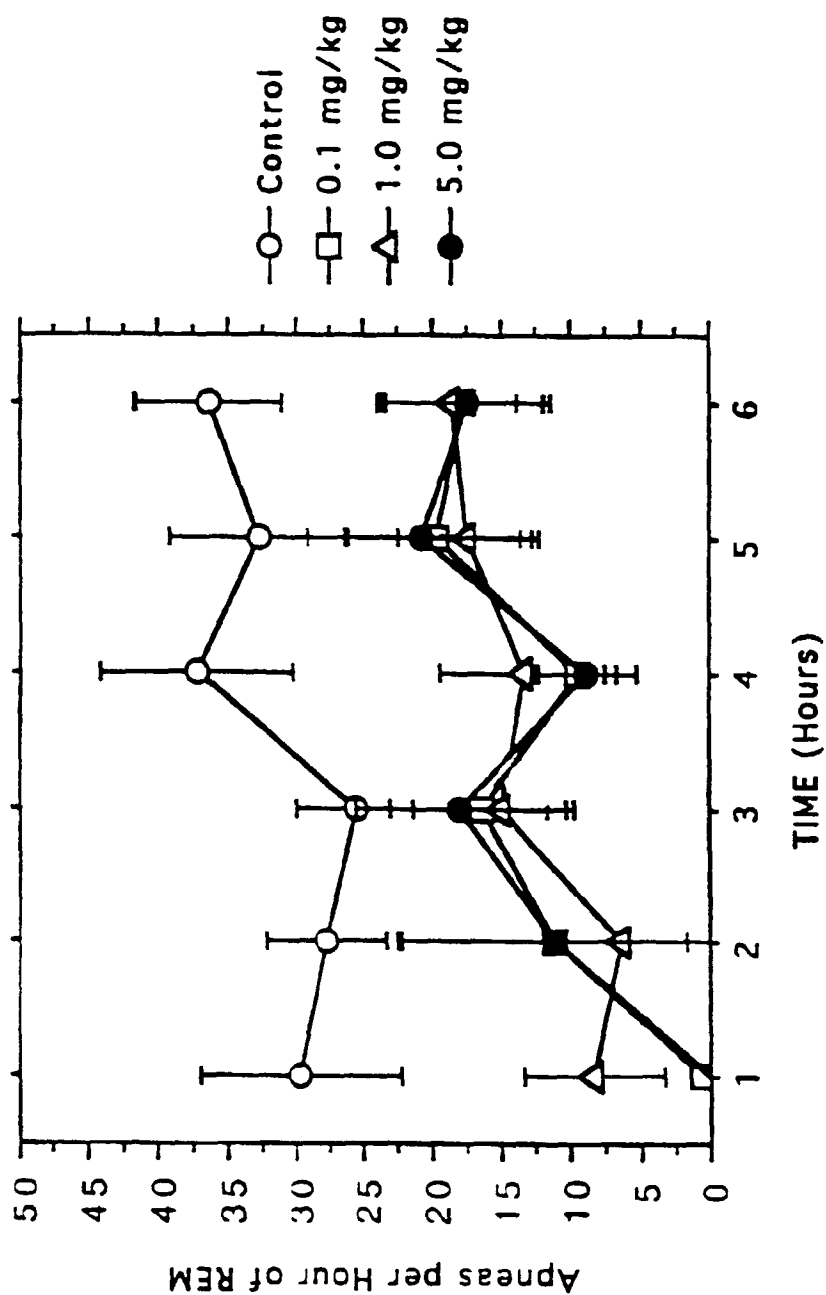


FIGURE 6

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FIGURE 7



PHARMACOLOGICAL TREATMENT FOR SLEEP APNEA

[0001] Priority is claimed to U.S. patent application Ser. No. 10/016,901, filed Dec. 14, 2001, which claims priority to U.S. patent application Ser. No. 09/622,823, filed Aug. 23, 2000, now U.S. Pat. No. 6,331,536 issued Dec. 18, 2001, which claims priority International Patent Appl. No. PCT/US99/04347, filed Feb. 26, 1999, which claims priority to U.S. Provisional Pat. App. Ser. No. 60/076,216, all of which are incorporated herein by reference in their entirety.

BACKGROUND OF THE INVENTION

[0002] 1. Field of the Invention

[0003] This invention generally relates to methods for the pharmacological treatment of breathing disorders and, more specifically, to the administration of agents or compositions having serotonin-related receptor activity for the alleviation of sleep apnea (central and obstructive) and other sleep-related breathing disorders.

[0004] 2. Related Technology

[0005] Over the past several years much effort has been devoted to the study of a discrete group of breathing disorders that occur primarily during sleep with consequences that may persist throughout the waking hours in the form of sleepiness, thereby manifesting itself into substantial economic loss (e.g., thousands of lost man-hours) or employment safety factors (e.g., employee non-attentiveness during operation of heavy-machinery). Sleep-related breathing disorders are characterized by repetitive reduction in breathing (hypopnea), periodic cessation of breathing (apnea), or a continuous or sustained reduction in ventilation.

[0006] In general sleep apnea is defined as an intermittent cessation of airflow at the nose and mouth during sleep. By convention, apneas of at least 10 seconds in duration have been considered important, but in most individuals the apneas are 20-30 seconds in duration and may be as long as 2-3 minutes. While there is some uncertainty as to the minimum number of apneas that should be considered clinically important, by the time most individuals come to attention of the medical community they have at least 10 to 15 events per hour of sleep.

[0007] Sleep apneas have been classified into three types: central, obstructive, and mixed. In central sleep apnea the neural drive to all respiratory muscles is transiently abolished. In obstructive sleep apneas, airflow ceases despite continuing respiratory drive because of occlusion of the oropharyngeal airway. Mixed apneas, which consist of a central apnea followed by an obstructive component, are a variant of obstructive sleep apnea. The most common type of apnea is obstructive sleep apnea.

[0008] Obstructive sleep apnea syndrome (OSAS) has been identified in as many as 24% of working adult men and 9% of similar women, with peak prevalence in the sixth decade. Habitual heavy snoring, which is an almost invariant feature of OSAS, has been described in up to 24% of middle aged men, and 14% of similarly aged women, with even greater prevalence in older subjects.

[0009] Obstructive sleep apnea syndrome's definitive event is the occlusion of the upper airway, frequently at the

level of the oropharynx. The resultant apnea generally leads to a progressive-type asphyxia until the individual is briefly aroused from the sleeping state, thereby restoring airway patency and thus restoring airflow.

[0010] An important factor that leads to the collapse of the upper airway in OSAS is the generation of a critical subatmospheric pressure during the act of inspiration that exceeds the ability of the airway dilator and abductor muscles to maintain airway stability. Sleep plays a crucial role by reducing the activity of the muscles of the upper airways including the dilator and abductor muscles.

[0011] In most individuals with OSAS the patency of the airway is also compromised structurally and is therefore predisposed to occlusion. In a minority of individuals the structural compromise is usually due to obvious anatomic abnormalities, i.e., adenotonsillar hypertrophy, retrognathia, or macroglossia. However, in the majority of individuals predisposed to OSAS, the structural abnormality is simply a subtle reduction in airway size, i.e., "pharyngeal crowding." Obesity also frequently contributes to the reduction in size seen in the upper airways. The act of snoring, which is actually a high-frequency vibration of the palatal and pharyngeal soft tissues that results from the decrease in the size of the upper airway lumen, usually aggravates the narrowing via the production of edema in the soft tissues.

[0012] The recurrent episodes of nocturnal asphyxia and of arousal from sleep that characterize OSAS lead to a series of secondary physiologic events, which in turn give rise to the clinical complications of the syndrome. The most common manifestations are neuropsychiatric and behavioral disturbances that are thought to arise from the fragmentation of sleep and loss of slow-wave sleep induced by the recurrent arousal responses. Nocturnal cerebral hypoxia also may play an important role. The most pervasive manifestation is excessive daytime sleepiness. OSAS is now recognized as a leading cause of daytime sleepiness and has been implicated as an important risk factor for such problems as motor vehicle accidents. Other related symptoms include intellectual impairment, memory loss, personality disturbances, and impotence.

[0013] The other major manifestations are cardiorespiratory in nature and are thought to arise from the recurrent episodes of nocturnal asphyxia. Most individuals demonstrate a cyclical slowing of the heart during the apneas to 30 to 50 beats per minute, followed by tachycardia of 90 to 120 beats per minute during the ventilatory phase. A small number of individuals develop severe bradycardia with asystoles of 8 to 12 seconds in duration or dangerous tachyarrhythmias, including unsustained ventricular tachycardia. OSAS also aggravates left ventricular failure in patients with underlying heart disease. This complication is most likely due to the combined effects of increased left ventricular afterload during each obstructive event, secondary to increased negative intrathoracic pressure, recurrent nocturnal hypoxemia, and chronically elevated sympathoadrenal activity.

[0014] Central sleep apnea is less prevalent as a syndrome than OSAS, but can be identified in a wide spectrum of patients with medical, neurological, and/or neuromuscular disorders associated with diurnal alveolar hypoventilation or periodic breathing. The definitive event in central sleep apnea is transient abolition of central drive to the ventilatory

muscles. The resulting apnea leads to a primary sequence of events similar to those of OSAS. Several underlying mechanisms can result in cessation of respiratory drive during sleep. First are defects in the metabolic respiratory control system and respiratory neuromuscular apparatus. Other central sleep apnea disorders arise from transient instabilities in an otherwise intact respiratory control system.

[0015] Many healthy individuals demonstrate a small number of central apneas during sleep, particularly at sleep onset and in REM sleep. These apneas are not associated with any physiological or clinical disturbance. In individuals with clinically significant central sleep apnea, the primary sequence of events that characterize the disorder leads to prominent physiological and clinical consequences. In those individuals with central sleep apnea alveolar hypoventilation syndrome, daytime hypercapnia and hypoxemia are usually evident and the clinical picture is dominated by a history of recurrent respiratory failure, polycythemia, pulmonary hypertension, and right-sided heart failure. Complaints of sleeping poorly, morning headache, and daytime fatigue and sleepiness are also prominent. In contrast, in individuals whose central sleep apnea results from an instability in respiratory drive, the clinical picture is dominated by features related to sleep disturbance, including recurrent nocturnal awakenings, morning fatigue, and daytime sleepiness.

[0016] Currently, the most common and most effective treatment, for adults with sleep apnea and other sleep-related breathing disorders are mechanical forms of therapy that deliver positive airway pressure (PAP). Under PAP treatment, an individual wears a tight-fitting plastic mask over the nose when sleeping. The mask is attached to a compressor, which forces air into the nose creating a positive pressure within the patient's airways. The principle of the method is that pressurizing the airways provides a mechanical "splinting" action, which prevents airway collapse and therefore, obstructive sleep apnea. Although an effective therapeutic response is observed in most patients who undergo PAP treatment, many patients cannot tolerate the apparatus or pressure and refuse treatment. Moreover, recent covert monitoring studies clearly demonstrate that long-term compliance with PAP treatment is very poor.

[0017] A variety of upper airway and craniofacial surgical procedures have been attempted for treatment of OSAS. Adenotonsillectomy appears to be an effective cure for OSAS in many children, but upper airway surgery is rarely curative in adult patients with OSAS. Surgical "success" is generally taken to be a 50% reduction in apnea incidence and there are no useful screening methods to identify the individuals that would benefit from the surgery versus those who would not derive a benefit.

[0018] Pharmacological treatments of several types have been attempted in patients with sleep apnea but, thus far, none have proven to be generally useful. A recent systematic review of these attempts is provided by Hudgel [*J. Lab. Clin. Med.*, 126:13-18 (1995)]. A number of compounds have been tested because of their expected respiratory stimulant properties. These include (1) acetazolamide, a carbonic anhydrase inhibitor that produced variable improvement in individuals with primary central apneas but caused an increase in obstructive apneas, (2) medroxyprogesterone, a progestin that has demonstrated no consistent benefit in

OSAS, and (3) theophylline, a compound usually used for the treatment of asthma, which may benefit patients with central apnea but appears to be of no use in adult patients with obstructive apnea.

[0019] Other attempted pharmacological treatment includes the administration of adenosine, adenosine analogs and adenosine reuptake inhibitors (U.S. Pat. No. 5,075,290). Specifically, adenosine, which is a ubiquitous compound within the body and which levels are elevated in individuals with OSAS, has been shown to stimulate respiration and is somewhat effective in reducing apnea in an animal model of sleep apnea.

[0020] Other possible pharmacological treatment options for OSAS include agents that stimulate the brain activity or are opioid antagonists. Specifically, since increased cerebral spinal fluid opioid activity has been identified in OSAS, it is a logical conclusion that central stimulants or opioid antagonists would be a helpful treatment of OSAS. In reality, doxapram, which stimulates the central nervous system and carotid body chemoreceptors, was found to decrease the length of apneas but did not alter the average arterial oxygen saturation in individuals with obstructive sleep apnea. The opioid antagonist naloxone, which is known to stimulate ventilation was only slightly helpful in individuals with obstructive sleep apnea.

[0021] Because OSAS is strongly correlated with the occurrence of hypertension, agents such as angiotensin-converting enzyme (ACE) inhibitors may be of benefit in treating OSAS individuals with hypertension but this does not appear to be a viable treatment for OSAS itself.

[0022] Finally, several agents that act on neurotransmitters and neurotransmitter systems involved in respiration have been tested in individuals with OSAS. Most of these compounds have been developed as anti-depressant medications that work by increasing the activity of monoamine neurotransmitters including norepinephrine, dopamine, and serotonin. Protriptyline, a tricyclic anti-depressant, has been tested in several small trials with variable results and frequent and significant side effects. As serotonin may promote sleep and stimulate respiration, tryptophan, a serotonin precursor and selective serotonin reuptake inhibitors have been tested in individuals with OSAS. While a patent has been issued for the use of the serotonin reuptake inhibitor, fluoxetine (U.S. Pat. No. 5,356,934), initial evidence suggests that these compounds may yield measurable benefits in only approximately 50% of individuals with OSAS. Therefore in view of the fact that the only viable treatment for individuals suffering from sleep-related breathing disorders is a mechanical form of therapy (PAP) for which patient compliance is low, and that hopes for pharmacological treatments have yet to come to fruition, there remains a need for simple pharmacologically-based treatments that would offer benefits to a broad base of individuals suffering from a range of sleep-related breathing disorders. There also remains a need for a viable treatment of sleep-related breathing disorders that would lend itself to a high rate of patient compliance.

SUMMARY OF THE INVENTION

[0023] The invention is directed to providing pharmacological treatments for the prevention or amelioration of sleep-related breathing disorders.

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[0024] The present invention is directed to methods for the prevention or amelioration of sleep-related breathing disorders, the method comprising the administration of an effective dose of serotonin receptor antagonist to a patient in need of such therapy. The present invention is also directed to methods comprising the administration of a combination of serotonin receptor antagonists for the prevention or amelioration of sleep-related breathing disorders. The combination of serotonin receptor antagonists may be directed to a single serotonin receptor subtype or to more than one serotonin receptor subtype.

[0025] The present invention is further directed to methods comprising the administration of a combination of serotonin receptor antagonists in conjunction with a combination of serotonin receptor agonists for the prevention or amelioration of sleep-related breathing disorders. The combination of serotonin receptor antagonists as well as the combination of receptor agonist may be directed to a single serotonin receptor subtype or to more than one serotonin receptor subtype.

[0026] The present invention is also directed to methods comprising the administration of a combination of serotonin receptor antagonists in conjunction with a α_2 adrenergic receptor subtype antagonist for the prevention or amelioration of sleep-related breathing disorders. The combination of serotonin receptor antagonists may be directed to a single serotonin receptor subtype or to more than one serotonin receptor subtype.

[0027] Routes of administration for the foregoing methods may be by any systemic means including oral, intraperitoneal, subcutaneous, intravenous, intramuscular, transdermal, or by other routes of administration. Osmotic mini-pumps and timed-released pellets or other depot forms of administration may also be used. The only limitation being that the route of administration results in the ultimate delivery of the pharmacological agent to the appropriate receptor.

[0028] Sleep-related breathing disorders include, but are not limited to, obstructive sleep apnea syndrome, apnea of prematurity, congenital central hypoventilation syndrome, obesity hypoventilation syndrome, central sleep apnea syndrome, Cheyne-Stokes respiration, and snoring.

[0029] A serotonin receptor antagonist can be used in its free base form or as a quaternary ammonium salt form. The quaternization of these serotonin receptor antagonists occurs by conversion of tertiary nitrogen atom into a quaternary ammonium salt with reactive alkyl halides such as, for example, methyl iodide, ethyl iodide, or various benzyl halides. Some quaternary forms of a serotonin antagonist, specifically, methylated zatosetron, has been shown to lack the ability to cross the blood-brain barrier (Gidda et al., *J. Pharmacol. Exp. Ther.* 273:695-701 (1995)), and thus only works on the peripheral nervous system. A serotonin receptor antagonist is defined by the chemical compound itself and one of its pharmaceutically acceptable salts.

[0030] Exemplary serotonin receptor antagonists include, but are not limited to, the free base form or a quaternized form of zatosetron, tropisetron, dolasetron, hydrodolasetron, mescaline, oxetorone, homochlorcyclizine, perlapine, ondansetron (GR38032F), ketanserin, loxapine, olanzapine, chlorpromazine, haloperidol, r (+) ondansetron, cisapride, norcisapride, (+) cisapride, (-) cisapride, (+) norcisapride,

(-) norcisapride, desmethylolanzapine, 2-hydroxymethylolanzapine, 1-(2-fluorophenyl)-3-(4-hydroxyaminoethyl)-prop-2-en-1-one-O-(2-dimethylaminoethyl)-oxime, risperidone, cyproheptadine, clozapine, methysergide, granisetron, mianserin, ritanserin, cinanserin, LY-53,857, metegoline, LY-278,584, methiothepin, p-NPPL, NAN-190, piperazine, SB-206553, SDZ-205,557, 3-tropanyl-indole-3-carboxylate, 3-tropanyl-indole-3-carboxylate methiodide, and other serotonin receptor antagonists and their quaternized forms or one of its pharmaceutically acceptable salts.

[0031] Exemplary serotonin receptor agonists include, but are not limited to 8-OH-DPAT, sumatriptan, L694247 (2-[5-[3-(4-methylsulfonylamino)benzyl-1,2,4-oxadiazol-5-yl]-1H-indol-3-yl]ethanamine), buspirone, alnitidan, zalospiro, ipsapirone, gepirone, zolmitriptan, risatriptan, 311C90, α -Me-5-IT, BW723C86 (1-[5(2-thienylmethoxy)-1H-3-indolyl]propan-2-amine hydrochloride), and MCPP (m-chlorophenylpiperazine). A serotonin receptor agonist is defined by the chemical compound itself and one of its pharmaceutically acceptable salts.

[0032] Exemplary α_2 adrenergic receptor antagonist include, but are not limited to phenoxybenzamine, phentolamine, tolazoline, terazosine, doxazosin, trimazosin, yohimbine, indoramin, ARC239, and prazosin or one of its pharmaceutically acceptable salts.

[0033] Exemplary selective serotonin reuptake inhibitors include, but are not limited to, fluoxetine, paroxetine, fluvoxamine, sertraline, citalopram, norfluoxetine, r(-) fluoxetine, s(+) fluoxetine, demethylsertraline, demethylcitalopram, venlafaxine, milnacipran, sibutramine, nefazodone, R-hydroxynefazodone, (-)venlafaxine, and (+) venlafaxine. A selective serotonin reuptake inhibitor is defined by the chemical compound itself and one of its pharmaceutically acceptable salts.

BRIEF DESCRIPTION OF THE DRAWINGS

[0034] FIG. 1 illustrates the effect of serotonin antagonist GR38032F (ondansetron) on the rate of apneas per hour of non-rapid eye movement (NREM) sleep as compared to control. Each data point on the figure represents the mean $\pm$ the standard error for 9 rats ($p=0.007$ versus control).

[0035] FIG. 2 shows the effect of the serotonin antagonist GR38032F (ondansetron) on the percentage of total recording time spent in NREM sleep as compared to control. Each data point represents the mean $\pm$ the standard error for 9 rats ($p=0.0001$ versus control).

[0036] FIG. 3 shows the effect of the serotonin antagonist GR38032F (ondansetron) on the rate of apneas per hour of rapid-eye-movement (REM) sleep as compared to control. Each data point represents the mean $\pm$ the standard error for 9 rats ($p=0.01$ versus control).

[0037] FIG. 4 illustrates the effect of the serotonin antagonist GR38032F (ondansetron) on the percentage of total recording time spent in REM sleep as compared to control. Each data point represents the mean $\pm$ the standard error for 9 rats.

[0038] FIG. 5 shows the effects of the serotonin antagonist GR38032F (ondansetron) on the rate of normalized minute ventilation during wakefulness, NREM and REM sleep as compared to control. Each data bar represents the mean $\pm$ the

standard error over 6 recording hours with all animals (n=9) pooled (minute ventilation was significantly larger following GR38032F administration in all behavioral states; $p < 0.03$ versus control).

[0039] FIG. 6 shows the effects of serotonin (0.79 mg/kg), GR38032F (0.1 mg/kg)+serotonin (0.79 mg/kg), and GR38032F (0.1 mg/kg) on spontaneous apneas in NREM sleep. Each data bar represents the mean $\pm$ the standard error over 6 recording hours with all animals (n=10; $p = 0.97$).

[0040] FIG. 7 illustrates the effects of serotonin (0.79 mg/kg), GR38032F (0.1 mg/kg)+serotonin (0.79 mg/kg), and GR38032F (0.1 mg/kg) on spontaneous apneas during REM sleep. Each data bar represents the mean $\pm$ the standard error over 6 recording hours with all animals (n=10; $p = 0.01$ for serotonin administration vs. control; $p = 0.05$ for administration of GR38032F+serotonin vs. serotonin alone; $p = 0.99$ for administration of GR38032F+serotonin vs. control; and $p = 0.51$ for administration of GR38032F alone).

DETAILED DESCRIPTION OF THE INVENTION

[0041] Previous studies on the effect of serotonin or serotonin analogs on respiration in several anesthetized (see below) animal species have demonstrated variable responses. For example, administration of serotonin has been shown to cause an increase in the respiratory rate with a decrease in tidal volume in rabbits, but an increase in the tidal volume in dogs [Matsumoto, *Arch. Int. Pharmacodyn. Ther.*, 254:282-292 (1981); Armstrong et al., *J. Physiol. (Lond.)*, 365:104 P (1985); Bisgard et al., *Resp. Physiol.* 37:61-80 (1979); Zucker et al. *Circ. Res.* 47:509-515 (1980). In studies with cats, serotonin administration produced hyperventilation occasionally preceded by apnea [Black et al., *Am. J. Physiol.*, 223:1097-1102 (1972); Jacobs et al., *Circ. Res.*, 29:145-155 (1971)], or immediate apnea followed by rapid shallow breathing [Szereda-Przestaszewska et al., *Respir. Physiol.*, 101:231-237 (1995)].

[0042] Administration of 2-methyl-5-hydroxytryptamine, a selective 5-hydroxytryptamine₃ receptor agonist, in cat studies caused apnea [Butler et al. *Br. J. Pharmacol.*, 94:397-412 (1988)]. Intravenous administration of serotonin, 2-methyl-5-hydroxytryptamine or a high dose of α -methyl-5-hydroxytryptamine, a 5-hydroxytryptamine₂ receptor agonist, produced transient apnea, the duration of which increased in a dose-dependent fashion. This response was significantly antagonized by GR38032F (1,2,3,9-tetrahydro-9-methyl-3-[(2-methylimidazol-1-yl)methyl]carbazole-4-one, hydrochloride, dihydrate), a selective 5-hydroxytryptamine₃ receptor antagonist [Butler et al. *Br. J. Pharmacol.*, 94:397-412 (1988); Hagan et al., *Eur. J. Pharmacol.*, 138:303-305 (1987)] as well as by ketanserin and methysergide, 5-hydroxytryptamine₂ receptor antagonists [Yoshioka et al., *J. Pharmacol. Exp. Ther.*, 260:917-924 (1992)]. In newborn rats, administration of serotonin precursor L-tryptophan, which activated central serotonin biosynthesis, produced recurrent episodes of obstructive apnea often followed by central apneas [Hilaire et al., *J. Physiol.*, 466:367-382 (1993); Morin, *Neurosci. Lett.*, 160:61-64 (1993)].

[0043] While the foregoing studies revealed significant information concerning the involvement of serotonin in the development of apneas, as stated above one significant

problem with all of these studies is that the animals were anesthetized, and thus any results obtained could not be attributed to a specific serotonin agonist or antagonist, i.e., an interaction with the anesthesia or abnormal physiologic conditions associated with the anesthetic could not be ruled out.

[0044] Activity at serotonin receptors may also promote spontaneous sleep-related central apneas, which have been reported in rats, [Mendelson et al., *Physiol. Behav.*, 43:229-234 (1988); Sato et al. *Am. J. Physiol.*, 259:R282-R287 (1990); Monti et al., *Pharmacol. Biochem. Behav.*, 125:131 (1995); Monti et al., *Pharmacol. Biochem. Behav.*, 53:341-345 (1996); Thomas et al., *J. Appl. Physiol.*, 78:215-218 (1992); Thomas et al., *J. Appl. Physiol.*, 73:1530-1536 (1995); Carley et al. *Sleep*, 19:363-366 (1996); Carley et al., *Physiol. Behav.*, 59:827-831 (1996); Radulovacki et al., *Sleep*, 19:767-773 (1996); Christon et al., *J. Appl. Physiol.*, 80:2102-2107 (1996)]. In order to test this hypothesis, experiments were conducted to test the effects of a serotonin antagonist in freely moving animals in order to assess whether blockade of serotonin receptors would inhibit expression of spontaneous apneas during NREM sleep and REM sleep. Experiments were also conducted to test the effects of serotonin and serotonin antagonists, singly and in combination, in freely moving animals in order to assess whether increased serotonergic activity at peripheral serotonin receptors may promote sleep apneas.

[0045] The following examples illustrate the effects of administration of serotonin receptor antagonists, and in particular GR38032F, to cause suppression of central apneas during non rapid eye movement (NREM) and especially during rapid eye movement (REM) sleep. This effect was associated with increased respiratory drive but did not cause cardiovascular changes at the dose tested.

[0046] The following examples also illustrate the effects of serotonin administration to induce spontaneous apnea expression, which was completely antagonized via the administration of serotonin receptor antagonists, and in particular GR38032F.

[0047] The following examples further describe the pharmacological profiles best suited for single agents or combinations of agents to successfully prevent or ameliorate sleep-related breathing disorders, i.e.,

[0048] (a) a single agent or combination of agents having either 5-hydroxytryptamine₂ or 5-hydroxytryptamine₃ receptor subtype antagonistic activity or both;

[0049] (b) a single agent or combination of agents having either 5-hydroxytryptamine₂ or 5-hydroxytryptamine₃ receptor subtype antagonistic activity or both in conjunction with either 5-hydroxytryptamine₁ or 5-hydroxytryptamine₂ receptor subtype agonistic activity or both; or

[0050] (c) a single agent or combination of agents having either 5-hydroxytryptamine₂ or 5-hydroxytryptamine₃ receptor subtype antagonistic activity or both in conjunction with α_2 adrenergic receptor subtype antagonistic activity.

[0051] Further aspects of the invention and embodiments will be apparent to those skilled in the art. In order that the

present invention is fully understood, the following examples are provided by way of exemplification only and not by way of limitation.

[0052] Example 1 describes the preparation of the animals for treatment with either serotonin antagonists or agonists or both and subsequent physiological recording and testing.

[0053] Example 2 describes the methods for the physiological recording of treatment and control animals and results obtained from administration of a serotonin antagonist.

[0054] Example 3 describes results obtained from the administration of serotonin followed by the administration of a serotonin receptor antagonist.

[0055] Example 4 describes agents or compositions that possess a specific serotonin-related pharmacological activity that is used to effectively suppress or prevent sleep-related breathing disorders.

[0056] The following examples are illustrative of aspects of the present invention but are not to be construed as limiting.

EXAMPLE 1

Preparation of Animals for Physiological Testing and Recording

[0057] Adult, male Sprague-Dawley rats (Sasco-King, Wilmington, Mass.; usually 8 per test group; 300 g) were maintained on a 12-hour light (08:00-20:00 hour)/12-hour dark (20:00-08:00 hour) cycle for one week, housed in individual cages and given ad libitum access to food and water. Following the one week of acclimatization, animals were subjected to the following surgical procedures.

[0058] Acclimatized animals were anesthetized for the implantation of cortical electrodes for electroencephalogram (EEG) recording and neck muscle electrodes for electromyogram (EMG) recording using a mixture of ketamine (Vedco, Inc., St. Joseph, Mo.; 100 mg/ml) and acetylpromazine (Vedco, Inc., St. Joseph, Mo.; 10 mg/ml; 4:1, volume/volume) at a volume of 1 ml/kg body weight. The surface of the skull was exposed surgically and cleaned with a 20% solution of hydrogen peroxide followed by a solution of 95% isopropyl alcohol. Next, a dental preparation of sodium fluoride (Flura-GEL®, Saslow Dental, Mt. Prospect, Ill.) was applied to harden the skull above the parietal cortex and allowed to remain in place for 5 minutes. The fluoride mixture was then removed from the skull above the parietal cortex. The EEG electrodes consisting of four stainless steel machine screws, having leads attached thereto, were threaded into the skull to rest on the dura over the parietal cortex. A thin layer of Justi® resin cement (Saslow Dental, Mt. Prospect, Ill.) was applied to cover the screw heads (of screws implanted in the skull) and surrounding skull to further promote the adhesion of the implant. EMG electrodes consisting of two ball-shaped wires were inserted into the bilateral neck musculature. All leads (i.e., EEG and EMG leads) were soldered to a miniature connector (39F1401, Newark Electronics, Schaumburg, Ill.). Lastly, the entire assembly was fixed to the skull with dental cement.

[0059] After surgery, all animals were allowed to recover for one week before being subjected to another surgery that

involved implantation of a radiotelemetry transmitter (TA11-PXT, Data Sciences International, St. Paul, Minn.) for monitoring blood pressure (BP) and heart period (HP), estimated as pulse interval. After the animals were anesthetized (as described above), the hair from the subxiphoid space to the pelvis was removed. The entire area was scrubbed with iodine and rinsed with alcohol and saline. A 4-6 cm midline abdominal incision was made to allow good visualization of the area from the bifurcation of the aorta to the renal arteries. A retractor was used to expose the contents of the abdomen and the intestine was held back using saline moistened gauze sponges. The aorta was dissected from the surrounding fat and connective tissues using sterile cotton applicators. A 3-0 silk suture was placed beneath the aorta and traction was applied to the suture to restrict the blood flow. Then the implant (TA11-PXT) was held by forceps while the aorta was punctured just cranial to the bifurcation using a 21-gauge needle bent at the beveled end. The tip of the catheter was inserted under the needle using the needle as a guide until the thin-walled BP sensor section was within the vessel. Finally, one drop of tissue adhesive (Vetbond®, 3M, Minneapolis, Minn.) was applied to the puncture site and covered with a small square of cellulose fiber (approximately 5 mm²) so as to seal the puncture after catheter insertion. The radio implant was attached to the abdominal wall by 3-0 silk suture, and the incision was closed in layers. After the second surgery, animals were again allowed a one week recovery period prior to administration of the serotonin receptor antagonist and subsequent physiological recording.

EXAMPLE 2

Physiological Recording and Suppression of Apneas

[0060] Physiological parameters (see below) from each animal were recorded on 2 occasions in random order, with recordings for an individual animal separated for at least 3 days. Fifteen minutes prior to each recording each animal received a systemic injection (1 ml/kg intraperitoneal bolus injection) of either saline (control) or 1 mg/kg of ondansetron (GR38032F; 1,2,3,9-tetrahydro-9-methyl-3-[(2-methylimidazol-1-yl)methyl]carbazole-4-one, hydrochloride, dihydrate; Glaxo Wellcome, Inc., Research Triangle Park, N.C.). Polygraphic recordings were made from hours 10:00-16:00.

[0061] Respiration was recorded by placing each animal, unrestrained, inside a single chamber plethysmograph (PLYUN1R/U; Buxco Electronics, Sharon, Conn.; dimension 6 in.x10 in.x6 in.) ventilated with a bias flow of fresh room air at a rate of 2 L/min. A cable plugged onto the animal's connector and passed through a sealed port was used to carry the bioelectrical activity from the head implant. Respiration, blood pressure, EEG activity, and EMG activity were displayed on a video monitor and simultaneously digitized 100 times per second and stored on computer disk (Experimenter's Workbench; Datawave Technologies, Longmont, Colo.).

[0062] Sleep and waking states were assessed using the biparietal EEG and nuchal EMG signals on 10-second epochs as described by Bennington et al. [*Sleep*, 17:28-36 (1994)]. This software discriminated wakefulness (W) as a high frequency low amplitude EEG with a concomitant high

EMG tone, NREM sleep by increased spindle and theta activity together with decreased EMG tone, and REM sleep by a low ratio of a delta to theta activity and an absence of EMG tone. Sleep efficiency was measured as the percentage of total recorded epochs staged as NREM or REM sleep.

[0063] An accepted physiological animal model [rat; Monti, et al., *Pharmacol. Biochem. Behav.*, 51:125-131 (1995)] of spontaneous sleep apnea was used to assess the effects of GR38032F. More specifically, sleep apneas, defined as cessation of respiratory effort for at least 2.5 seconds, were scored for each recording session and were associated with the stage of sleep in which they occurred: NREM or REM sleep. The duration requirement of 2.5 seconds represented at least 2 "missed" breaths, which is therefore analogous to a 10 second apnea duration requirement in humans, which also reflects 2-3 missed breaths. The events detected represent central apneas because decreased ventilation associated with obstructed or occluded airways would generate an increased plethysmographic signal, rather than a pause. An apnea index (AI), defined as apneas per hour in a stage were separately determined for NREM and REM sleep. The effects of sleep stage (NREM vs. REM) and injection (control vs. GR38032F) were tested using ANOVA with repeated measures. Multiple comparisons were controlled using Fisher's protected least significant difference (PLSD). In addition, the timing and volume of each breath were scored by automatic analysis (Experimenters' Workbench; Datawave Technologies, Longmont, Colo.). For each animal the mean respiratory rate (RR) and minute ventilation (MV) was computed for W throughout the 6 hour control recording and used as a baseline to normalize respiration during sleep and during GR38032F administration in that animal. One way ANOVA was also performed by non-parametric (Kruskal-Wallis) analysis. Conclusions using parametric and non-parametric ANOVA were identical in all cases.

[0064] Similar software (Experimenters' Workbench; Datawave Technologies, Longmont, Colo.) was employed to analyze the blood pressure waveform; for each beat of each recording, systolic (SBP) and diastolic (DBP) blood pressures and pulse interval were measured. The pulse interval provided a beat by beat estimate of IIP. Mean BP (MBP) was estimated according to the weighted average of SBP and DBP for each beat: $MBP = DBP + (SBP - DBP)/3$. The parameters for each beat were also classified according to the sleep/wake state and recording hour during which they occurred.

[0065] Results of the administration of the serotonin antagonist GR38032F on the rate of apneas per hour of NREM sleep during the 6 hours of polygraphic recording (see FIG. 1) demonstrated no significant effect of treatment or time over 6 hours (two-way ANOVA). However, there was a significant suppression of apneas during the first 2 hours of recording as determined by paired t-tests ($p < 0.01$ for each). This respiratory effect was associated with a significant suppression of NREM sleep by the GR38032F during the first 2 hours as demonstrated in FIG. 2. The percentage of NREM sleep in 6 hour recordings was lower in GR38032F administered rats than in controls, but the decrease reached statistical significance only during the first 2 hours of the recordings ($p < 0.001$).

[0066] Results further indicated a significant suppressant effect of GR38032F on REM sleep apneas throughout the 6

hour recording period ($p = 0.01$ for drug effect on 2-way ANOVA; see FIG. 3). This effect was particularly manifest during the first 4 hours of recordings, during which no animal exhibited a single spontaneous apnea in REM sleep. This effect was not a simple reflection of REM suppression during the first 4 hours.

[0067] Results set forth in FIG. 4 show that GR38032F did not significantly affect REM sleep. Although REM sleep in drug treated animals was lower than in corresponding controls it did not reach statistical significance overall or during any single recording hour.

[0068] Results of the administration of GR38032F on the normalized minute ventilation during W (wake), NREM (non-rapid eye movement) sleep, and REM (rapid eye movement) sleep (see FIG. 5) indicate a significant stimulation of ventilation during all behavioral states ($p = 0.03$ for each). Finally, results indicate that GR38032F had no effect on any cardiovascular variable (MBP and HP during W, NREM, and REM sleep) measured ($p > 0.1$ for each variable; see Table 1).

TABLE 1

	Effects of GR38032F on Cardiovascular Variables					
	Mean BP (mm Hg)			HP (msec)		
	W	NREM	REM	W	NREM	REM
Control	111 ± 18	110 ± 18	108 ± 18	174 ± 5	181 ± 5	185 ± 6
GR38032F	113 ± 18	112 ± 17	110 ± 17	183 ± 3	189 ± 3	190 ± 3

All values are mean ± SE.

[0069] Overall these results indicate that the manipulation of serotonergic systems can exert a potent influence on the generation of central apneas in both REM and NREM sleep. Specifically the present findings indicate that systemic administration of a 5-hydroxytryptamine₃ receptor antagonist suppresses spontaneous apnea expression; completely abolishing REM-related apnea for at least 4 hours after intraperitoneal injection. This apnea suppression was associated with a generalized respiratory stimulation that was observed as increased minute ventilation during both waking and sleep. These significant respiratory effects were observed at a dose which caused no change in heart rate or blood pressure, even during the first 2 hours, when respiration was maximal.

[0070] Those of skill in the art will recognize that exemplary serotonin receptor antagonists in its free base form or as a quaternary ammonium salt include, but are not limited to (a) ketanserin, cinanserin, LY-53,857, metergoline, LY-278,584, methiothepin, p-NPPL, NAN-190, piperazine, SB-206553, SDZ-205,557, 3-tropanyl-indole-3-carboxylate, 3-tropanyl-indole-3-carboxylate methiodide, methysergide (Research Biochemicals, Inc., Natick, Mass.); (b) risperidone (Janssen Pharmaceutica, Titusville, N.J.); (c) cyproheptadine, clozapine, mianserin, ritanserin (Sigma Chemical Co., St. Louis, Mo.); (d) ondansetron, granisetron (SmithKline Beecham, King of Prussia, Pa.), zatosetron, tropisetron, dolasetron, and hydrodolasetron; (e) loxapine, olanzapine, chlorpromazine, haloperidol, (+) ondansetron, cisapride, norcisapride, (+) cisapride, (-) cisapride, (+)

norcispapride, (-) norcispapride, desmethyloanzapine, 2-hydroxymethylanzapine, 1-(2-fluorophenyl)-3-(4-hydroxyaminoethyl)-prop-2-en-1-one-O-(2-dimethylaminoethyl)-oxime, (f) mescaline, oxetorone, homochlorcyclizine, and perlapine and other serotonin receptor antagonists and any of their quaternary form or pharmaceutically acceptable salts may be used to prevent or ameliorate sleep-related breathing disorders. Further, those of skill in the art will also recognize that the results discussed above may be easily correlated to other mammals, especially primates (e.g., humans).

EXAMPLE 3

Induction and Suppression of Sleep Apneas

[0071] Administration of serotonin or serotonin analogs produced variable respiratory responses in anesthetized animals of several species (see above, DETAILED DESCRIPTION OF THE INVENTION). As shown above in Example 2, intraperitoneal administration of 1 mg/kg GR38032F, a selective 5-hydroxytryptamine₃ receptor antagonist, suppressed spontaneous central apneas. This effect was especially prominent in REM sleep, during which apneas were completely abolished for at least 4 hours following injection. The apnea suppressant effect of GR38032F was paralleled by increased respiratory drive, but BP and heart rate changes were absent at the dose tested.

[0072] Suppression of spontaneous apneas during natural sleep by GR38032F (see Example 2) is consistent with prior studies in anesthetized rats, wherein 5-hydroxytryptamine and 2-methyl-5-hydroxytryptamine, a selective 5-HT₃ receptor agonist, provoked central apneas that were antagonized by GR38032F. Since 5-hydroxytryptamine does not penetrate the blood-brain barrier (BBB), these results (from the prior studies) indicate that stimulation of peripheral 5-hydroxytryptamine receptors, and more particularly 5-hydroxytryptamine₃ receptors seemed to have provoked the occurrence of central apneas. In view of that study, performed in anesthetized animals, as well as our study (described in Example 2 above) in freely moving rats with respect to administration of GR38032F, we studied the ability of increased serotonergic activity at peripheral 5-hydroxytryptamine receptors, and more specifically, 5-hydroxytryptamine₃ receptors to promote spontaneous sleep-related central apneas and whether any induction of apneas would be susceptible to antagonism by administration of 5-hydroxytryptamine receptor antagonists.

[0073] Ten adult male Sprague-Dawley rats (Sasco-King, Wilmington, Mass.; 300 g) were maintained on a 12-h light (08:00-20:00 hour)/12-hour dark (20:00-08:00) cycle for one week, housed in individual cages, and given ad libitum access to food and water. Following the one week of acclimatization, animals were prepared for physiological testing via the surgical procedures (i.e., implantation of cortical electrodes for EEG recording and neck muscle electrodes for EMG recording, implantation of a radiotelemetry transmitter for BP and HP monitoring) as set forth above in Example 1. After completion of the surgical procedures, animals were allowed a one week recovery period prior to use in the present study.

[0074] Each animal was recorded on four occasions, with recordings for an individual animal separated by at least

three days. Fifteen minutes prior to each recording, each animal received (via intraperitoneal injection), in random order, one of the following: (a) saline solution (control); (b) 0.79 mg/kg serotonin; (c) 0.1 mg/kg GR38032F plus 0.79 mg/kg serotonin; or (d) 0.1 mg/kg GR38032F. For the GR38032F+serotonin test group, 0.1 mg/kg GR38032F was administered at time 09:30 followed by 0.79 mg/kg serotonin at time 09:45. Polygraphic recordings were made from 10:00-16:00.

[0075] Respiration BP, EEG, and EMG data were determined and recorded via the experimental procedure as specifically set forth above in Example 2. As in Example 2, sleep apneas, defined as cessation of respiratory effort for at least 2.5 s, were scored for each recording session and were associated with the stage in which they occurred: NREM or REM sleep. The duration requirement of 2.5 s represents at least two "missed" breaths, which is analogous to a 10-s apnea duration requirement in humans.

[0076] The effects of sleep stage (NREM vs REM) and injection (control vs. administration of either serotonin alone, GR38032F+serotonin, or GR38032F alone) on apnea indexes, respiratory pattern, BP, and HP were tested using analysis of variance (ANOVA) with repeated measures. Multiple comparisons were controlled using Fisher's protected least-significance difference (PLSD). One-way ANOVA was also performed by nonparametric (Kruskal-Wallis) analysis. Conclusions using parametric and nonparametric ANOVA were identical in all cases.

[0077] Results of the administration of either serotonin alone (0.79 mg/kg), GR38032F (0.1 mg/kg)+serotonin (0.79 mg/kg), or GR38032F alone (0.1 mg/kg) on the ability to promote spontaneous apneas in NREM sleep during a 6 hour polygraphic recording is set forth in FIG. 6. Specifically, during NREM sleep, the spontaneous apnea index was not affected by any drug treatment.

[0078] As illustrated in FIG. 7, spontaneous apnea expression during REM sleep significantly increased following administration of serotonin as compared to control recording (>250% increase). Results also indicate that such an increase was abolished via prior administration of GR38032F. At the low dose tested (0.1 mg/kg) administration of GR38032F alone had no effect on REM sleep spontaneous apneas.

[0079] As set forth in Table 2 (percentages of waking, NREM, and REM sleep during 6 hours of polygraphic recording following drug administration), intraperitoneal administration of serotonin alone, GR38032F+serotonin, or GR38032F alone had no effect on sleep architecture. Finally, no treatment group tested had a significant effect on RR, VE, mean BP, HP, or PS apnea index (data not shown).

TABLE 2

Effects of 5-HT and GR38032F on Sleep/Wake Architecture			
	% Wakefulness	% NREM	% REM
Control (saline solution)	33.7 ± 2.5*	58.0 ± 1.9	6.9 ± 1.1
5-HT (0.79 mg/kg)	30.2 ± 3.2	59.9 ± 3.3	6.5 ± 1.1
5-HT + GR38032F	36.7 ± 8.7	56.0 ± 7.6	5.3 ± 1.4
GR38032F (0.1 mg/kg)	28.8 ± 6.4	63.4 ± 5.7	7.3 ± 2.3
p (1-way ANOVA)	0.43	0.71	0.60

*All values reflect means ± SE for percent recording time.

[0080] Overall these results indicate that manipulation of peripheral serotonin receptors exerts a potent influence on the generation of central apneas during REM sleep. Specifically, the present results show that systemic administration of serotonin increases spontaneous apnea expression in sleep. Although the dose of serotonin employed had no effect on sleep, cardiovascular variables, RR, or VE, the REM-related spontaneous apnea index increased >250%. Further, it is important to note that the mechanisms of apnea genesis are at least partially sleep-state specific, as NREM apneas were unaffected.

[0081] These findings demonstrate that exogenous administration of 5-hydroxytryptamine₃ agonists and antagonists at various doses produces changes in apnea expression that are specific to REM sleep. Such findings indicate that there is a physiologic role for endogenous serotonergic activity in modulating the expression of apnea, especially during REM sleep. Moreover, because serotonin does not cross the blood-brain barrier, the finding that serotonin exerts a converse effect to GR38032F indicates that the relevant receptors are located in the peripheral nervous system. Further, the present data suggest that the action of supraphysiologic levels of serotonin on apneas is receptor mediated in that pretreatment with a low dose (0.1 mg/kg) of GR38032F, which had no independent effect on any measured parameter, including apneas, fully blocked the effects of exogenous serotonin on apnea expression.

[0082] In view of the foregoing data, the likely peripheral site of action for the observed apnea-promoting effects of serotonin administration is thought to be the nodose ganglia of the vagus nerve. More specifically, several studies have concluded that the apnea component of the Bezold-Jarisch reflex results from the action of serotonin at the nodose ganglia in cats [Jacobs et al., *Circ. Res.*, 29:145-155 (1971), Sampson et al., *Life Sci.*, 15:2157-2165 (1975), Sutton, *Pflugers Arch.*, 389:181-187 (1981)] and rats [Yoshioka et al., *J. Pharmacol. Exp. Ther.*, 260:917-924 (1992) and McQueen et al., *J. Physiol.*, 507:843-855 (1998)]. Intravenous administration of serotonin or 5-hydroxytryptamine₃ receptor agonists also stimulates pulmonary vagal receptors [McQueen et al., *J. Physiol.*, 507:843-855 (1998)], which may contribute significantly to the apneic response.

[0083] Although species differences may be present [Black et al., *Am. J. Physiol.*, 223:1097-1102 (1972)], several studies in rat demonstrate that, in addition to its impact on vagal signaling, serotonin also elicits increased firing from carotid body chemoreceptors [McQueen et al., *J. Physiol.*, 507:843-855 (1998); Sapru et al., *Res. Comm. Chem. Pathol. Pharmacol.*, 16:245-250 (1977); Yoshioka, *J. Pharmacol. Exp. Ther.*, 250:637-641 (1989) and Yoshioka et al., *Res. Comm. Chem. Pathol. Pharmacol.*, 74:39-45 (1991)] and increased VE [McQueen et al., *J. Physiol.*, 507:843-855 (1998); Sapru et al., *Res. Comm. Chem. Pathol. Pharmacol.*, 16:245-250 (1977)]. Although chemoreceptor-mediated effects on apnea cannot be ruled out, the data of McQueen et al., *J. Physiol.*, 507:843-855 (1998) strongly indicate that intravenous serotonin elicits apnea via a vagal pathway, while the chemoreceptor activation opposes apnea genesis in the anesthetized rat.

[0084] The serotonin-induced Bezold-Jarisch reflex in anesthetized animals includes apnea and bradycardia. At the dose employed, serotonin did not elicit changes in either

heart rate or mean BP over the 6 hour recording period. Beat-to-beat heart rate and BP variability, assessed as coefficients of variation, were also unaffected by serotonin at the dose tested. The observed dissociation of cardiovascular and respiratory responses to serotonin indicates that changes in apnea expression were not baroreceptor mediated.

[0085] Although the Bezold-Jarisch reflex in anesthetized animals and serotonin-induced apneas in REM sleep are not the same phenomenon, they may be related by similar mechanisms. When serotonin receptors are strongly manipulated by exogenous means, i.e., either with serotonergic agonists or antagonists, the expression of spontaneous apneas in REM sleep can be amplified or suppressed. However, our observation that 1 mg/kg GR38032F significantly suppressed REM apneas does not preclude a role for 5-hydroxytryptamine₂ or other 5-hydroxytryptamine receptor subtypes in the peripheral regulation of the apnea expression, and in fact the invention also contemplates the use of 5-hydroxytryptamine₂ and 5-hydroxytryptamine₃, alone or in combination as well as serotonin antagonists that exhibit both type 2 and type 3 receptor antagonism (see Example 4).

[0086] It has been well established [Mendelson et al., *Physiol. Behav.*, 43:229-234 (1988); Sato et al., *Am. J. Physiol.*, 259:R282-287 (1990); Monti et al., *Pharmacol. Biochem. Behav.*, 51:125-131 (1995); Monti et al., *Pharmacol. Biochem. Behav.*, 53:341-345 (1996); Thomas et al., *J. Appl. Physiol.*, 73:1530-1536 (1992) and Thomas et al., *J. Appl. Physiol.*, 78:215-218 (1995)] that apnea frequency in rats increases from deep slow-wave sleep to light NREM sleep to REM sleep, as is the case in man. The high incidence of apnea expression during REM sleep may be related to respiratory changes that take place during this sleep state. Typically, during REM sleep, breathing becomes shallow and irregular [Orem et al., *Respir. Physiol.*, 30:265-289 (1977); Phillipson, *Annu. Rev. Physiol.*, 40:133-156 (1978); Sieck et al., *Exp. Neurol.*, 67:79-102 (1980) and Sullivan, In: Orem et al., eds., "Physiology in sleep," Academic Press, New York, N.Y., pp. 213-272 (1980)] and VE is at its lowest point [Hudgel et al., *J. Appl. Physiol.*, 56:133-137 (1984)]. This background of low respiratory output coupled with strong phasic changes in autonomic activity [Mancia et al., In: Orem et al., eds., "Physiology in sleep," Academic Press, New York, N.Y., pp. 1-55 (1980)] would render respiratory homeostasis during REM sleep more vulnerable to interruption by apnea. Thus it is possible that the role of serotonin activity in the peripheral nervous system in REM apnea genesis may arise from a serotonergic modulation of either tonic or phasic activity of respiratory afferent activity, especially in the vagus nerves. Therefore, the brainstem respiratory integrating areas may be rendered more vulnerable to fluctuating afferent inputs during REM sleep.

[0087] Overall, the results presented herein indicate that the exacerbation of spontaneous apnea during REM sleep produced by peripherally administered serotonin is receptor mediated. Such findings also indicate a physiologic role for endogenous serotonin in the peripheral nervous system in modulating sleep apnea expression under baseline conditions.

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EXAMPLE 4

Suppression or Prevention of Sleep Apneas

[0088] As indicated by the data presented herein (see Examples 2 and 3) serotonin plays an important and integral role in apnea genesis, which is both highly site and receptor subtype specific. More specifically, the efficacy of a serotonin receptor antagonist to suppress apnea is based on its activity in the peripheral nervous system, with the nodose ganglia of the vagus nerves appearing to be a crucial target site. 5-hydroxytryptamine₂ and 5-hydroxytryptamine₃ receptors at this site are clearly implicated in serotonin-induced apnea in anesthetized animals [Yoshioka et al., *J. Pharmacol. Exp. Therp.*, 260:917-924 (1992)]. In conjunction with these previous findings, the data presented herein (that administration of serotonin strictly to the peripheral nervous system exacerbates sleep-related apnea) indicates the importance of nodose ganglion serotonin receptors of both types in sleep apnea pathogenesis. Moreover, the serotonin-induced increase in apnea expression was completely blocked by a low dose of GR38032F, a 5-hydroxytryptamine₃ antagonist. Such a result indicates that the previously demonstrated suppression of apnea by GR38032F (see Example 2) most probably resulted from activity in the peripheral nervous system.

[0089] Therefore, in view of the foregoing, sleep related breathing disorders (sleep apnea syndrome, apnea of infancy, Cheyne-Stokes respiration, sleep-related hypoventilation syndromes) may be effectively prevented or suppressed via systemic administration of pharmacological agents exhibiting either serotonin type 2 or type 3 receptor antagonism, alone or in combination as well as agents that exhibit both serotonin type 2 and type 3 receptor antagonism.

[0090] Effective treatments for the prevention or suppression of sleep-related breathing disorders include systemic administration of a 5-hydroxytryptamine₂ or 5-hydroxytryptamine₃ receptor antagonist either alone or in combination. In a preferred embodiment the serotonin receptor antagonist has activity only in the peripheral nervous system and/or does not cross the blood-brain barrier. In a more preferred embodiment the serotonin receptor antagonist displays both 5-hydroxytryptamine₂ and 5-hydroxytryptamine₃ receptor subtype antagonism.

[0091] Current pharmacological treatments for sleep-related breathing disorders also involve apnea suppression via serotonin agonist effects within the central nervous system, and more specifically the brainstem. Indeed, it was in view of their potential to stimulate respiration and upper airway motor outputs that serotonin enhancing drugs were originally tested as pharmacological treatments for sleep apnea syndrome. One early report suggested that L-tryptophan, a serotonin precursor, may have a beneficial effect on sleep apnea syndrome [Schmidt, *Bull. Eur. Physiol. Respir.*, 19:625-629 (1982)]. More recently fluoxetine [Hanzel et al., *Chest.*, 100:416-421 (1991)] and paroxetine [Kraicz et al., *Sleep*, 22:61-67 (1999)], both selective serotonin reuptake inhibitors (SSRIs), were demonstrated to benefit some but not all patients with sleep apnea syndrome. In addition, combinations of serotonin precursors and reuptake inhibitors reduced sleep disordered respiration in English bulldog model of sleep apnea syndrome [Veasey et al., *Sleep Res.*,

A529;1997 and Veasey et al., *Am. J. Resp. Crit. Care Med.*, 157:A655 (1997)]. However, despite ongoing investigations these encouraging early results with serotonin enhancing drugs have not been reproduced.

[0092] The foregoing efforts with serotonin-enhancing drugs indicate that the potential utility of serotonin precursors or SSRIs in apnea treatment resides strictly in their central nervous system effects. Therefore, it is precisely because the serotonin enhancing effects of SSRIs in the peripheral nervous have been left unchecked that these compounds have not demonstrated reproducible effects in apnea treatment. In fact buspirone, a specific 5-hydroxytryptamine_{1A} agonist, which stimulates respiration [Mendelson et al., *Am. Rev. Respir. Dis.*, 141:1527-1530 (1990)], has been shown to reduce apnea index in 4 of 5 patients with sleep apnea syndrome [Mendelson et al., *J. Clin. Psychopharmacol.*, 11:71-72 (1991)] and to eliminate post-surgical apneustic breathing in one child [Wilken et al., *J. Pediatr.*, 130:89-94 (1997)]. Although buspirone acts systemically, 5-hydroxytryptamine₂ receptors in the peripheral nervous system have not been shown to play a role in apnea genesis. The modest apnea suppression induced by buspirone is a central nervous system effect that goes unopposed by serotonergic effects in the peripheral nervous system.

[0093] The rationale for using SSRIs such as fluoxetine or paroxetine to treat sleep apnea syndrome rests in part on their ability to stimulate upper airway motor outputs. Applications of serotonin to the floor of the fourth ventricle [Rose et al., *Resp. Physiol.*, 101:59-69 (1995)] or into the hypoglossal motor nucleus [Kubin et al., *Neurosci. Lett.*, 139:243-248 (1992)] produce upper airway motor activation in cats; effects which appear to be mediated predominantly by 5-hydroxytryptamine₂ receptors. Conversely, systemic administration of 5-hydroxytryptamine₂ receptor antagonists to English bulldogs reduces electrical activation of upper airway muscles, diminishes upper airway cross-sectional area and promotes obstructive apnea [Veasey et al., *Am. J. Crit. Care Med.*, 153:776-786 (1996)]. These observations provide a likely explanation for the improvements in sleep-disordered breathing observed in some patients following SSRI treatment.

[0094] In conjunction with the data presented herein (Examples 2 and 3) and the foregoing observations, sleep related breathing disorders (sleep apnea syndrome, apnea of infancy, Cheyne-Stokes respiration, sleep-related hypoventilation syndromes) may be effectively prevented or suppressed via systemic administration of

[0095] (a) an agent or combinations of agents exhibiting either serotonin type 2 or type 3 receptor antagonism (either alone or in combination with one another) and/or in combination with either a 5-hydroxytryptamine₁ or 5-hydroxytryptamine₂ receptor agonist;

[0096] (b) an agent or combination of agents or agents that exhibit both serotonin type 2 and type 3 receptor antagonism in combination with either a 5-hydroxytryptamine₁ or 5-hydroxytryptamine₂ receptor agonist; or

[0097] (c) agents that exhibit both the proper antagonistic and agonistic pharmacological profile (i.e., an agent that is both an agonist and antagonist at the receptor subtypes set forth above).

[0098] Preferred embodiments include the following:

[0099] (a) an agent or combination of agents wherein the serotonin agonist exhibits only central serotonergic actions;

[0100] (b) an agent or combination of agents wherein the serotonin agonist exhibits only central 5-hydroxytryptamine₂ actions;

[0101] (c) an agent or combination of agents wherein the serotonin antagonist exhibits only peripheral actions while the serotonin agonist exhibits only central serotonergic actions;

[0102] (d) an agent or combination of agents that have the ability to induce central nervous system serotonin release and that possess the antagonistic profile discussed above (i.e. both a 5-hydroxytryptamine₂ and 5-hydroxytryptamine₃ receptor antagonist); or

[0103] (e) an agent or combination of agents that have the ability to induce central nervous system serotonin release and possess only peripheral antagonistic effects;

[0104] Those of skill in the art will recognize that many serotonin receptor agonists such as, but not limited to 8-OH-DPAT (8-hydroxy-2-(di-n-propylamino)tetralin, sumatriptan, L694247 (2-[5-[3-(4-methylsulphonylamino)benzyl-1,2,4-oxadiazol-5-yl]-1H-indol-3yl]ethanamine), buspirone, alnitidan, zalospirone, ipsapirone, gepirone, zolmitriptan, risatriptan, 311C90, α -Me-5-HT, BW723C86 (1-[5(2-thienylmethoxy)-1H-3-indolyl]propan-2-amine hydrochloride), MCPP (m-chlorophenylpiperazine), as well as others may be used in conjunction with serotonin receptor antagonists to prevent or ameliorate sleep-related breathing disorders.

[0105] Pharmacological mechanisms of action other than serotonin precursors or SSRIs may also be exploited to enhance central nervous system serotonin activity. Indeed, at least one mechanism allows augmented serotonin release to be selectively targeted at the central nervous system. Specifically, antagonism of presynaptic α_2 adrenergic receptors located on brainstem serotonergic neurons (heteroreceptors) enhances serotonin release. Selective 5-hydroxytryptamine₂ and 5-hydroxytryptamine₃ receptor antagonists have been shown to block presynaptic α_2 -adrenoreceptors as well as postsynaptic 5-hydroxytryptamine₂ and 5-hydroxytryptamine₃ receptors [deBoer, *J. Clin. Psychiatr.*, 57(4): 19-25 (1996); Devane, *J. Clin. Psychiatry*, 59(20):85-93 (1998); and Puzantian, *Am. J. Health-Syst. Pharm.*, 55:44-49 (1998)]. Because the affinity of such agents for central α_2 receptors is 10 times higher than for peripheral α_2 receptors [Puzantian, *Am. J. Health-Syst. Pharm.*, 55:44-49 (1998)], central serotonin release is increased with minimal adrenergic side effects such as hypertension. Thus because these pharmacological agents are high affinity antagonists at 5-hydroxytryptamine_{2A}, 5-hydroxytryptamine_{2C}, and 5-hydroxytryptamine₃ receptors, the net effect is increased post-synaptic 5-hydroxytryptamine₁ activity within the brain and reduced 5-hydroxytryptamine₂ and 5-hydroxytryptamine₃ post-synaptic activity in the central and peripheral nervous systems. Each of these pharmacological effects serve to stimulate respiration and suppress apnea.

[0106] In view of the foregoing observations, sleep related breathing disorders (sleep apnea syndrome, apnea of infancy, Cheyne-Stokes respiration, sleep-related hypoventilation syndromes) may also be effectively suppressed or prevented via systemic administration of pharmacological agents of combinations of agents having α_2 adrenergic antagonist activity with either serotonin type 2 or type 3 receptor antagonist activity (either alone or in combination with one another). Preferred embodiments include:

[0107] (a) an agent or combination of agents wherein the α_2 adrenergic antagonist effects are exerted centrally;

[0108] (b) an agent or combination of agents wherein the serotonin antagonist effects are exerted peripherally;

[0109] (c) an agent or combination of agents wherein the α_2 adrenergic antagonist effects are exerted centrally and the serotonin antagonist effects are exerted peripherally;

[0110] (d) the agent or combination of agents of embodiments a-c wherein the α_2 adrenergic antagonist effect is exerted presynaptically;

[0111] (e) the agent or combination of agents of embodiments a-d wherein the α_2 adrenergic antagonist effects are exerted selectively at presynaptic heteroreceptors on serotonergic neurons; or

[0112] (f) the agent or combination of agents of embodiments a-d in which the α_2 adrenergic antagonist effect is exerted by an agent or combination of agents possessing the following pharmacological profile: α_2 adrenergic antagonist activity with both serotonin type 2 or type 3 receptor antagonist activity.

[0113] Those of skill in the art will recognize that many α_2 adrenergic receptor antagonists such as, but not limited to phenoxybenzamine, phentolamine, tolazoline, terazosine, doxazosin, trimazosin, yohimbine, indoramin, ARC239, prazosin as well as others may be used in conjunction with serotonin receptor antagonists to prevent or ameliorate sleep-related breathing disorders

[0114] An individual diagnosed with a sleep-related breathing disorder is administered either a composition or agent having any of the foregoing pharmacological profiles in an amount effective to prevent or suppress such disorders. The specific dose may be calculated according to such factors as body weight or body surface. Further refinement of the calculations necessary to determine the appropriate dosage for treatment of sleep-related breathing disorders is routinely made by those of ordinary skill in the art without undue experimentation. Appropriate dosages may be ascertained through use of established assays for determining dosages. Routes of administration for the foregoing methods may be by any systemic means including oral, intraperitoneal, subcutaneous, intravenous, intramuscular, transdermal, or by other routes of administration. Osmotic mini-pumps and timed-released pellets or other depot forms of administration may also be used.

[0115] Finally, those of skill in the art will recognize that with respect to the compounds discussed above, such compounds may contain a center of chirality. Thus such agents

may exist as different enantiomers of enantiomeric mixtures. Use of any one enantiomer alone or contained within an enantiomeric mixture with one or more stereoisomers is contemplated by the present invention.

[0116] Although the present invention has been described in terms of preferred embodiments, it is intended that the present invention encompass all modifications and variations that occur to those skilled in the art upon consideration of the disclosure herein, and in particular those embodiments that are within the broadest proper interpretation of the claims and their requirements. All literature cited herein is incorporated by reference.

What is claimed is:

1. A method of preventing or ameliorating a sleep-related breathing disorder comprising administering to a patient in need thereof an effective amount of at least one serotonin receptor antagonist, in free base or quaternized form, selected from the group consisting of zatosetron, tropisetron, dolasetron, hydrodolasetron, mescaline, oxetorone, homochlorcyclizine, perlapine, loxapine, olanzapine, chlorpromazine, haloperidol, *r* (+) ondansetron, cisapride, norcisapride, (+) cisapride, (-) cisapride, (+) norcisapride, (-) norcisapride, desmethyloanzapine, 2-hydroxymethyloanzapine, and 1-(2-fluorophenyl)-3-(4-hydroxyaminoethyl)-prop-2-en-1-one-O-(2-dimethylaminoethyl)-oxime.

2. The method of claim 1 wherein the sleep-related breathing disorder is selected from the group consisting of obstructive sleep apnea syndrome, apnea of prematurity, congenital central hypoventilation syndrome, obesity hypoventilation syndrome, central sleep apnea syndrome, Cheyne-Stokes respiration, and snoring.

3. A method of preventing or ameliorating a sleep-related breathing disorder comprising administering to a patient in need thereof an effective amount of at least one serotonin receptor antagonist, in quaternized form, selected from the group consisting of ondansetron, ketanserin, risperidone, cyproheptadine, clozapine, methysergide, granisetron, mianserin, ritanserin, cinanserin, LY-53,857, metergoline, LY-278,584, methiothepin, p-NPPL, NAN-190, piperazine, SB-206553, SDZ-205,557, 3-tropanyl-indole-3-carboxylate, and 3-tropanyl-indole-3-carboxylate methiodide.

4. The method of claim 3 wherein the sleep-related breathing disorder is selected from the group consisting of obstructive sleep apnea syndrome, apnea of prematurity, congenital central hypoventilation syndrome, obesity hypoventilation syndrome, central sleep apnea syndrome, Cheyne-Stokes respiration, and snoring.

5. A method of preventing or ameliorating a sleep-related breathing disorder comprising administering to a patient in need thereof an effective amount of

(a) at least one of a serotonin receptor antagonist

(i) in free base or quaternized form selected from the group consisting of zatosetron, tropisetron, dolasetron, hydrodolasetron, mescaline, oxetorone, homochlorcyclizine, perlapine, loxapine, olanzapine, chlorpromazine, haloperidol, *r* (+) ondansetron, cisapride, norcisapride, (+) cisapride, (-) cisapride, (+) norcisapride, (-) norcisapride, desmethyloanzapine, 2-hydroxymethyloanzapine, and 1-(2-fluorophenyl)-3-(4-hydroxyaminoethyl)-prop-2-en-1-one-O-(2-dimethylaminoethyl)-oxime;;

(ii) in quaternized form selected from the group consisting of ondansetron, ketanserin, risperidone, cyproheptadine, clozapine, methysergide, granisetron, mianserin, ritanserin, cinanserin, LY-53,857, metergoline, LY-278,584, methiothepin, p-NPPL, NAN-190, piperazine, SB-206553, SDZ-205,557, 3-tropanyl-indole-3-carboxylate, and 3-tropanyl-indole-3-carboxylate methiodide; and

(iii) and mixtures thereof; and

(b) a serotonin receptor agonist.

6. The method of claim 5 wherein the serotonin receptor antagonist in the quaternized form is methylated, ethylated, or benzylated.

7. The method of claim 5 wherein the serotonin receptor agonist is selected from the group consisting of 8-OH-DPAT, sumatriptan, L694247, buspirone, almitidan, zalospiro, ipsapirone, gepirone, zolmitriptan, risatriptan, 311C90, α -Me-5-HT, BW723C86, and MCPP.

8. The method of claim 5 wherein the serotonin receptor agonist is a 5-hydroxytryptamine₁ receptor subtype agonist.

9. The method of claim 5 wherein the serotonin receptor agonist is a 5-hydroxytryptamine₂ receptor subtype agonist.

10. The method of claim 5 wherein the effects of the serotonin receptor agonist are exerted in the central nervous system.

11. The method of claim 5 wherein the effects of the serotonin receptor antagonist are exerted in the peripheral nervous system.

12. The method of claim 5 wherein the effects of the serotonin receptor agonist are exerted in the central nervous system and wherein the effects of the serotonin receptor antagonist are exerted in the peripheral nervous system.

13. A method of preventing or ameliorating a sleep-related breathing disorder comprising administering to a patient in need thereof an effective amount of

(a) at least one of a serotonin receptor antagonist

(i) in their free base or quaternized form selected from the group consisting of zatosetron, tropisetron, dolasetron, hydrodolasetron, mescaline, oxetorone, homochlorcyclizine, perlapine, loxapine, olanzapine, chlorpromazine, haloperidol, *r* (+) ondansetron, cisapride, norcisapride, (+) cisapride, (-) cisapride, (+) norcisapride, (-) norcisapride, desmethyloanzapine, 2-hydroxymethyloanzapine, 1-(2-fluorophenyl)-3-(4-hydroxyaminoethyl)-prop-2-en-1-one-O-(2-dimethylaminoethyl)-oxime;

(ii) and in their quaternized form selected from the group consisting of ondansetron, ketanserin, risperidone, cyproheptadine, clozapine, methysergide, granisetron, mianserin, ritanserin, cinanserin, LY-53,857, metergoline, LY-278,584, methiothepin, p-NPPL, NAN-190, piperazine, SB-206553, SDZ-205,557, 3-tropanyl-indole-3-20 carboxylate, and 3-tropanyl-indole-3-carboxylate methiodide; and

(iii) mixtures thereof; and

(b) an effective amount of a selective serotonin reuptake inhibitor.

14. The method of claim 13 wherein the selective serotonin reuptake inhibitor is selected from the group consisting of fluoxetine and paroxetine.

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15. The method of claim 13 wherein the selective serotonin reuptake inhibitor is selected from the group consisting of fluvoxamine, sertraline, citalopram, norfluoxetine, r(-) fluoxetine, s(+) fluoxetine, demethylsertraline, demethylcitalopram, venlafaxine, milnacipran, sibutramine, nefazodone, R-hydroxynefazodone, (-)venlafaxine, and (+) venlafaxine.

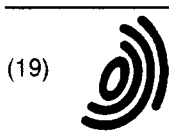
16. A method of preventing or ameliorating a sleep-related breathing disorder comprising administering to a patient in need thereof

(a) an effective amount of at least one serotonin receptor antagonist selected from the group consisting of zatosetron, tropisetron, dolasetron, hydrodolasetron, mescaline, oxetorone, homochlorcyclizine, perlapine, ondansetron (GR38032F), ketanserin, loxapine, olanzapine, chlorpromazine, haloperidol, r (+) ondansetron, cisapride, norcisapride, (+) cisapride, (-) cisapride, (+) norcisapride, (-) norcisapride, desmethylolanzapine,

2-hydroxymethylolanzapine, 1-(2-fluorophenyl)-3-(4-hydroxyaminoethyl)-prop-2-en-1-one-O-(2-dimethylaminoethyl)-oxime, risperidone, cyproheptadine, clozapine, methysergide, granisetron, mianserin, ritanserin, cinanserin, IY-53,857, metergoline, IY-278, 584, methiothepin, p-NPPL, NAN-190, piperazine, SB-206553, SDZ-205,557, 3-tropanyl-indole-3-carboxylate, and 3-tropanyl-indole-3-carboxylate methiodide; and

(b) at least one selective serotonin reuptake inhibitor selected from the group consisting of fluvoxamine, sertraline, fluoxetine, paroxetine, citalopram, norfluoxetine, r(-)fluoxetine, s(+)fluoxetine, demethylsertraline, demethylcitalopram, venlafaxine, minacipran, sibutramine, nefazodone, R-hydroxynefazodone, (-) venlafaxine, and (+)venlafaxine.

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(54) **Olanzapine (zyprexa) in combination with fluoxetine (prozac), lithium or anticonvulsant for therapy of refractory depression**

(57) The invention provides methods and compositions for the treatment of depressive states refractory to treatment with traditional anti-depressive therapies alone. These methods and compositions employ a compound having activity as an atypical antipsychotic and

a serotonin reuptake inhibitor. This invention also provides methods of providing rapid onset treatments of major depression which employing a compound having activity as an atypical antipsychotic and a serotonin reuptake inhibitor.

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Description

[0001] The present invention belongs to the fields of pharmacology, medicine and medicinal chemistry, and provides methods and compositions for treating refractory depression or partial responders.

5 [0002] Depression in its many variations has recently become much more visible to the general public than it has previously been. It is now recognized as an extremely damaging disorder, and one that afflicts a surprisingly large fraction of the population. Suicide is the most extreme symptom of depression, but millions of people, not quite so drastically afflicted, live in misery and partial or complete uselessness, and afflict their families as well by their affliction. The introduction of fluoxetine, a serotonin reuptake inhibitor (SRI), was a breakthrough in the treatment of depression, and depressives are now much more likely to be diagnosed and treated than they were only a decade ago.

10 [0003] Depression is often associated with other diseases and conditions, or caused by such other conditions. For example, it is associated with Parkinson's disease; with HIV infection; with Alzheimer's disease; and with abuse of anabolic steroids. Depression may also be associated with abuse of any substance, or may be associated with behavioral problems resulting from or occurring in combination with head injuries, mental retardation or stroke.

15 [0004] Despite the breakthrough nature of selective serotonin reuptake inhibitors in the treatment of depression, a number of patients suffering from major depression do not respond, or respond only partially to treatment with SRIs or other traditional modes of treating depression, including the older tricyclics. The present invention addresses this by offering methods of treating patients suffering from refractory depression, or partially responding. Additionally, as there is frequently a significant period of time before treatment with SRIs can have a therapeutic effect, this invention provides a therapeutic benefit in providing methods of treating depression by a more rapid onset, while attenuating adverse events frequently associated with conventional antidepressant medication.

20 [0005] The invention provides a method for treating a patient suffering from or susceptible to refractory depression, comprising administering to said patient an effective amount of a first component which is an atypical antipsychotic, in combination with an effective amount of a second component which is a serotonin reuptake inhibitor.

25 [0006] In addition, this invention provides a method for treating a patient partially responding to treatment for depression, which comprises administering to said patient an effective amount of a first component which is an atypical antipsychotic, in combination with an effective amount of a second component which is a serotonin reuptake inhibitor.

[0007] This invention provides, further, a method for attenuating adverse events associated with treating a patient suffering from or susceptible to refractory depression which comprises administering to said patient an effective amount of a first component which is an atypical antipsychotic, in combination with an effective amount of a second component which is a serotonin reuptake inhibitor.

30 [0008] This invention also provides a method of providing rapid onset treatment of depression to a patient which comprises administering to said patient an effective amount of a first component which is an atypical antipsychotic, in combination with an effective amount of a second component which is a serotonin reuptake inhibitor.

35 [0009] The invention also provides a pharmaceutical composition which comprises a first component which is an atypical antipsychotic, and a second component which is a serotonin reuptake inhibitor, the two compounds being present in an amount effective in the treatment of depression refractory to traditional pharmaceutical intervention.

[0010] By "partial response" is meant an improvement of less than 50% on the HAMD-21 or Montgomery-Asberg Depression Rating Scale, preferably from about 1% to about 49%; more preferably from about 10% to about 49%, most preferably from about 15% to about 49%.

40 [0011] The term "attenuating" means decreasing the number, severity or frequency of side effects or adverse events associated with treatment of depression with conventional antidepressant medication, including tricyclics and SSRIs, when such products are used at dosages that yield beneficial effects on the symptoms of the disease.

[0012] The term "activation" means agitation.

45 [0013] The term "sexual dysfunction" means a disturbance or variation in the pattern of human sexual response (excitement phase, plateau phase, orgasmic phase and resolution phase), Masters et al., *Human Sexual Response*, Little Brown and Company, Boston, 1966 and *Human Sexual Inadequacy*, Little Brown and Company, Boston, 1970. Included are disorders related to the erectile response in male mammals and the sexual desire and sexual (both arousal and orgasmic) reflexes in male or female mammals such as decreased libido, erectile dysfunction, retarded ejaculation and anorgasm.

50 [0014] In this document, all temperatures are described in degrees Celsius, and all amounts, ratios of amounts and concentrations are described in weight units unless otherwise stated.

The Compounds

55 [0015] In the general expressions of the present invention, the first component is a compound which acts as an atypical antipsychotic. The essential feature of an atypical antipsychotic is less acute extrapyramidal symptoms, especially dystonias, associated with therapy as compared to a typical antipsychotic such as haloperidol. Clozapine, the

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prototypical atypical antipsychotic, differs from the typical antipsychotics with the following characteristics: (1) greater efficacy in the treatment of overall psychopathology in patients with schizophrenia nonresponsive to typical antipsychotics; (2) greater efficacy in the treatment of negative symptoms of schizophrenia; and (3) less frequent and quantitatively smaller increases in serum prolactin concentrations associated with therapy (Beasley, et al., Neuropsychopharmacology, **14**(2), 111-123, (1996)). Atypical antipsychotics include, but are not limited to:

Olanzapine, 2-methyl-4-(4-methyl-1-piperazinyl)-OH-thieno[2,3-b][1,5]benzodiazepine, is a known compound and is described in U.S. Patent No. 5,229,382 as being useful for the treatment of schizophrenia, schizophreniform disorder, acute mania, mild anxiety states, and psychosis. U.S. Patent No. 5,229,382 is herein incorporated by reference in its entirety;

Clozapine, 8-chloro-11-(4-methyl-1-piperazinyl)-5H-dibenzo[b,e][1,4]diazepine, is described in U.S. Patent No. 3,539,573, which is herein incorporated by reference in its entirety. Clinical efficacy in the treatment of schizophrenia is described (Hanes, et al., Psychopharmacol. Bull., **24**, 62 (1988));

Risperidone, 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidino]ethyl]-2-methyl-6,7, 8,9-tetrahydro-4H-pyrido [1,2-a]pyrimidin-4-one, and its use in the treatment of psychotic diseases are described in U.S. Patent No. 4,804,663, which is herein incorporated by reference in its entirety;

Sertindole, 1-[2-[4-[5-chloro-1-(4-fluorophenyl)-1H-indol-3-yl]-1-piperidinyl]ethyl]imidazolidin-2-one, is described in U.S. Patent No. 4,710,500. Its use in the treatment of schizophrenia is described in U.S. Patent Nos. 5,112,838 and 5,238,945. U.S. Patent Nos. 4,710,500; 5,112,838; and 5,238,945 are herein incorporated by reference in their entirety;

Quetiapine, 5-[2-(4-dibenzo[b,f][1,4]thiazepin-11-yl-1-piperazinyl)ethoxy]ethanol, and its activity in assays which demonstrate utility in the treatment of schizophrenia are described in U.S. Patent No. 4,879,288, which is herein incorporated by reference in its entirety. Quetiapine is typically administered as its (E)-2-butenedioate (2:1) salt; and Ziprasidone, 5-[2-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]ethyl]-6-chloro-1,3-dihydro-2H-indol-2-one, is typically administered as the hydrochloride monohydrate. The compound is described in U.S. Patent Nos. 4,831,031 and 5,312,925. Its activity in assays which demonstrate utility in the treatment of schizophrenia are described in U.S. Patent No. 4,831,031. U.S. Patent Nos. 4,831,031 and 5,312,925 are herein incorporated by reference in their entirety.

[0016] Similarly, when the invention is regarded in its broadest sense, the second component compound is a compound which functions as a serotonin reuptake inhibitor. The measurement of a compound's activity in that utility is now a standard pharmacological assay. Wong, et al., Neuropsychopharmacology **8**, 337-344 (1993). Many compounds, including those discussed at length above, have such activity, and no doubt many more will be identified in the future. In the practice of the present invention, it is intended to include reuptake inhibitors which show 50% effective concentrations of about 1000 nM or less, in the protocol described by Wong *supra*. Serotonin reuptake inhibitors include, but are not limited to:

Fluoxetine, N-methyl-3-(p-trifluoromethylphenoxy)-3-phenylpropylamine, is marketed in the hydrochloride salt form, and as the racemic mixture of its two enantiomers.

U.S. Patent 4,314,081 is an early reference on the compound. Robertson et al., J. Med. Chem. **31**, 1412 (1988), taught the separation of the R and S enantiomers of fluoxetine and showed that their activity as serotonin uptake inhibitors is similar to each other. In this document, the word "fluoxetine" will be used to mean any acid addition salt or the free base, and to include either the racemic mixture or either of the R and S enantiomers;

Duloxetine, N-methyl-3-(1-naphthalenyloxy)-3-(2-thienyl)propanamine, is usually administered as the hydrochloride salt and as the (+) enantiomer. It was first taught by U.S. Patent 4,956,388, which shows its high potency. The word "duloxetine" will be used here to refer to any acid addition salt or the free base of the molecule;

Venlafaxine is known in the literature, and its method of synthesis and its activity as an inhibitor of serotonin and norepinephrine uptake are taught by U.S. Patent 4,761,501. Venlafaxine is identified as compound A in that patent; Milnacipran (N,N-diethyl-2-aminomethyl-1-phenylcyclopropanecarboxamide) is taught by U.S. Patent 4,478,836, which prepared milnacipran as its Example 4. The patent describes its compounds as antidepressants. Moret et al., Neuropharmacology **24**, 1211-19 (1985), describe its pharmacological activities as an inhibitor of serotonin and norepinephrine reuptake;

Citalopram, 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofurancarbonitrile, is disclosed in U.S. Patent 4,136,193 as a serotonin reuptake inhibitor. Its pharmacology was disclosed by Christensen et al., Eur. J. Pharmacol. **41**, 153 (1977), and reports of its clinical effectiveness in depression may be found in Dufour et al., Int. Clin. Psychopharmacol. **2**, 225 (1987), and Timmerman et al., *ibid.*, 239;

Fluvoxamine, 5-methoxy-1-[4-(trifluoromethyl)phenyl]-1-pentanone O-(2-aminoethyl)oxime, is taught by U.S. Patent 4,085,225. Scientific articles about the drug have been published by Claassen et al., Brit. J. Pharmacol. **60**,

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505 (1977); and De Wilde *et al.*, *J. Affective Disord.* **4**, 249 (1982); and Benfield *et al.*, *Drugs* **32**, 313 (1986); Paroxetine, trans-(-)-3-[(1,3-benzodioxol-5-yloxy)methyl]-4-(4-fluorophenyl)piperidine, may be found in U.S. Patents 3,912,743 and 4,007,196. Reports of the drug's activity are in Lassen, *Eur. J. Pharmacol.* **47**, 351 (1978); Hassan *et al.*, *Brit. J. Clin. Pharmacol.* **19**, 705 (1985); Laursen *et al.*, *Acta Psychiat. Scand.* **71**, 249 (1985); and Battegay *et al.*, *Neuropsychobiology* **13**, 31 (1985); and Sertraline, (1S-cis)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-N-methyl-1-naphthylamine hydrochloride, is a serotonin reuptake inhibitor which is marketed as an antidepressant. It is disclosed by U.S. Patent 4,536,518.

[0017] All of the U.S. patents which have been mentioned above in connection with compounds used in the present invention are incorporated herein by reference.

[0018] It will be understood that while the use of a single atypical antipsychotic as a first component compound is preferred, combinations of two or more atypical antipsychotics may be used as a first component if necessary or desired. Similarly, while the use of a single serotonin reuptake inhibitor as a second component compound is preferred, combinations of two or more serotonin reuptake inhibitors may be used as a second component if necessary or desired.

[0019] While all combinations of first and second component compounds are useful and valuable, certain combinations are particularly valued and are preferred, as follows:

olanzapine/fluoxetine
olanzapine/venlafaxine
olanzapine/citalopram
olanzapine/fluvoxamine
olanzapine/paroxetine
olanzapine/sertraline
olanzapine/milnacipran
olanzapine/duloxetine
clozapine/fluoxetine
risperidone/fluoxetine
sertindole/fluoxetine
quetiapine/fluoxetine
ziprasidone/fluoxetine

[0020] In general, combinations and methods of treatment using olanzapine as the first component are preferred. Furthermore, combinations and methods of treatment using fluoxetine as the second component are preferred. Especially preferred are combinations and methods of treatment using olanzapine as the first component and fluoxetine as the second component.

[0021] It is especially preferred that when the first component is olanzapine, it will be the Form II olanzapine polymorph having a typical x-ray powder diffraction pattern as represented by the following interplanar spacings:

	d
40	10.2689
	8.577
	7.4721
	7.125
45	6.1459
	6.071
	5.4849
	5.2181
	5.1251
50	4.9874
	4.7665
	4.7158
	4.4787
55	4.3307
	4.2294
	4.141
	3.9873

96
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(continued)

d

5

3.7206

3.5645

3.5366

3.3828

3.2516

10

3.134

3.0848

3.0638

3.0111

2.8739

15

2.8102

2.7217

2.6432

2.6007

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[0022] A typical example of an x-ray diffraction pattern for Form II is as follows wherein d represents the interplanar spacing and I/I_1 represents the typical relative intensities:

25

d	I/I_1
10.2689	100.00
8.577	7.96
7.4721	1.41
7.125	6.50
6.1459	3.12
6.071	5.12
5.4849	0.52
5.2181	6.86
5.1251	2.47
4.9874	7.41
4.7665	4.03
4.7158	6.80
4.4787	14.72
4.3307	1.48
4.2294	23.19
4.141	11.28
3.9873	9.01
3.7206	14.04
3.5645	2.27
3.5366	4.85
3.3828	3.47
3.2516	1.25
3.134	0.81
3.0848	0.45
3.0638	1.34
3.0111	3.51
2.8739	0.79
2.8102	1.47
2.7217	0.20
2.6432	1.26

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(continued)

d	I/I ₁
2.6007	0.77

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[0023] The x-ray diffraction patterns set out herein were obtained using a Siemens D5000 x-ray powder diffractometer having a copper K_α radiation source of wavelength, $\lambda = 1.541 \text{ \AA}$.

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[0024] It is further preferred that the Form II olanzapine polymorph will be administered as the substantially pure Form II olanzapine polymorph.

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[0025] As used herein "substantially pure" refers to Form II associated with less than about 5% Form I, preferably less than about 2% Form I, and more preferably less than about 1% Form I. Further, "substantially pure" Form II will contain less than about 0.5% related substances, wherein "related substances" refers to undesired chemical impurities or residual solvent or water. In particular, "substantially pure" Form II should contain less than about 0.05% content of acetonitrile, more preferably, less than about 0.005% content of acetonitrile. Additionally, the polymorph of the invention should contain less than 0.5% of associated water.

[0026] The polymorph obtainable by the process taught in the '382 patent will be designated as Form I and has a typical x-ray powder diffraction pattern substantially as follows, obtained using a Siemens D5000 x-ray powder diffractometer, wherein d represents the interplanar spacing:

20

d
9.9463
8.5579
8.2445
6.8862
6.3787
6.2439
5.5895
5.3055
4.9815
4.8333
4.7255
4.6286
4.533
4.4624
4.2915
4.2346
4.0855
3.8254
3.7489
3.6983
3.5817
3.5064
3.3392
3.2806
3.2138
3.1118
3.0507
2.948
2.8172
2.7589
2.6597
2.6336
2.5956

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[0027] A typical example of an x-ray diffraction pattern for Form I is as follows wherein d represents the interplanar spacing and I/I₁ represents the typical relative intensities:

	d	I/I ₁
5	9.9463	100.00
	8.5579	15.18
	8.2445	1.96
	6.8862	14.73
10	6.3787	4.25
	6.2439	5.21
	5.5895	1.10
	5.3055	0.95
15	4.9815	6.14
	4.8333	68.37
	4.7255	21.88
	4.6286	3.82
	4.533	17.83
20	4.4624	5.02
	4.2915	9.19
	4.2346	18.88
	4.0855	17.29
25	3.8254	6.49
	3.7489	10.64
	3.6983	14.65
	3.5817	3.04
	3.5064	9.23
30	3.3392	4.67
	3.2806	1.96
	3.2138	2.52
	3.1118	4.81
	3.0507	1.96
35	2.948	2.40
	2.8172	2.89
	2.7589	2.27
	2.6597	1.86
40	2.6336	1.10
	2.5956	1.73

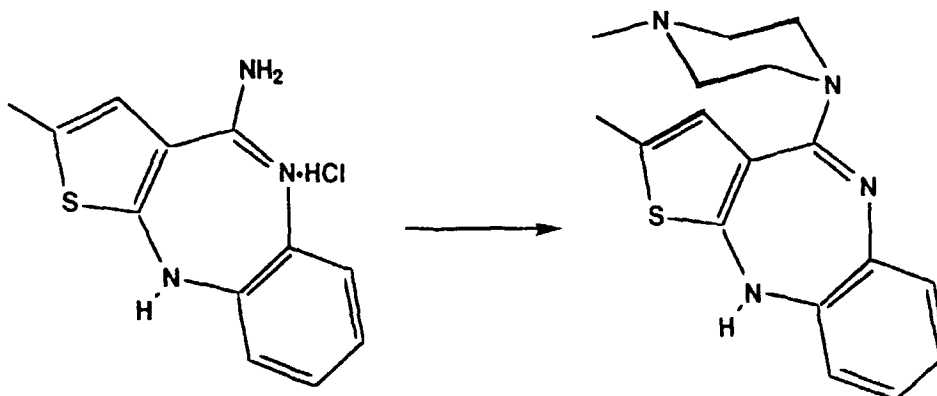
[0028] The x-ray powder diffraction patterns herein were obtained with a copper K_α of wavelength λ = 1.541Å. The interplanar spacings in the column marked "d" are in Angstroms. The typical relative intensities are in the column marked "I/I₁".

[0029] Though Form II olanzapine is preferred it will be understood that as used herein, the term "olanzapine" embraces all solvate and polymorphic forms unless specifically indicated.

Preparation 1

Technical Grade olanzapine

[0030]



Intermediate 1

[0031] In a suitable three neck flask the following was added:

Dimethylsulfoxide (analytical)	6 volumes
Intermediate 1	75 g
N-Methylpiperazine (reagent)	6 equivalents

Intermediate 1 can be prepared using methods known to the skilled artisan. For example, the preparation of the Intermediate 1 is taught in the above-referenced '382 patent.

[0032] A sub-surface nitrogen sparge line was added to remove the ammonia formed during the reaction. The reaction was heated to 120°C and maintained at that temperature throughout the duration of the reaction. The reactions were followed by HPLC until = 5% of the intermediate 1 was left unreacted. After the reaction was complete, the mixture was allowed to cool slowly to 20°C (about 2 hours). The reaction mixture was then transferred to an appropriate three neck round bottom flask and water bath. To this solution with agitation was added 10 volumes reagent grade methanol and the reaction was stirred at 20°C for 30 minutes. Three volumes of water was added slowly over about 30 minutes. The reaction slurry was cooled to zero to 5°C and stirred for 30 minutes. The product was filtered and the wet cake was washed with chilled methanol. The wet cake was dried in vacuo at 45°C overnight. The product was identified as technical olanzapine.

Yield: 76.7%; Potency: 98.1%

Preparation 2

Form II olanzapine polymorph

[0033] A 270 g sample of technical grade 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5]benzodiazepine was suspended in anhydrous ethyl acetate (2.7 L). The mixture was heated to 76°C and maintained at 76°C for 30 minutes. The mixture was allowed to cool to 25°C. The resulting product was isolated using vacuum filtration. The product was identified as Form II using x-ray powder analysis.

Yield: 197 g.

[0034] The process described above for preparing Form II provides a pharmaceutically elegant product having potency ≥ 97%, total related substances < 0.5% and an isolated yield of > 73%.

[0035] It will be understood by the skilled reader that most or all of the compounds used in the present invention are capable of forming salts, and that the salt forms of pharmaceuticals are commonly used, often because they are more readily crystallized and purified than are the free bases. In all cases, the use of the pharmaceuticals described above

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as salts is contemplated in the description herein, and often is preferred, and the pharmaceutically acceptable salts of all of the compounds are included in the names of them.

[0036] Many of the compounds used in this invention are amines, and accordingly react with any of a number of inorganic and organic acids to form pharmaceutically acceptable acid addition salts. Since some of the free amines of the compounds of this invention are typically oils at room temperature, it is preferable to convert the free amines to their pharmaceutically acceptable acid addition salts for ease of handling and administration, since the latter are routinely solid at room temperature. Acids commonly employed to form such salts are inorganic acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, phosphoric acid, and the like, and organic acids, such as p-toluenesulfonic acid, methanesulfonic acid, oxalic acid, p-bromophenylsulfonic acid, carbonic acid, succinic acid, citric acid, benzoic acid, acetic acid and the like. Examples of such pharmaceutically acceptable salts thus are the sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, chloride, bromide, iodide, acetate, propionate, decanoate, caprylate, acrylate, formate, isobutyrate, caproate, heptanoate, propiolate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, butyne-1,4-dioate, hexyne-1,6-dioate, benzoate, chlorobenzoate, methylbenzoate, dinitrobenzoate, hydroxybenzoate, methoxybenzoate, phthalate, sulfonate, xylenesulfonate, phenylacetate, phenylpropionate, phenylbutyrate, citrate, lactate, b-hydroxybutyrate, glycolate, tartrate, methanesulfonate, propanesulfonate, naphthalene-1-sulfonate, naphthalene-2-sulfonate, mandelate and the like. Preferred pharmaceutically acceptable salts are those formed with hydrochloric acid, oxalic acid or fumaric acid.

20 Administration

[0037] The dosages of the drugs used in the present invention must, in the final analysis, be set by the physician in charge of the case, using knowledge of the drugs, the properties of the drugs in combination as determined in clinical trials, and the characteristics of the patient, including diseases other than that for which the physician is treating the patient. General outlines of the dosages, and some preferred dosages, can and will be provided here. Dosage guidelines for some of the drugs will first be given separately; in order to create a guideline for any desired combination, one would choose the guidelines for each of the component drugs.

Olanzapine: from about 0.25 to 100 mg, once/day; preferred, from 1 to 30 mg, once/day; and most preferably 1 to 25 mg once/day;
Clozapine: from about 12.5 to 900 mg daily; preferred, from about 150 to 450 mg daily;
Risperidone: from about 0.25 to 16 mg daily; preferred from about 2-8 mg daily;
Sertindole: from about .0001 to 1.0 mg/kg daily;
Quetiapine: from about 1.0 to 40 mg/kg given once daily or in divided doses;
35 Ziprasidone: from about 5 to 500 mg daily; preferred from about 50 to 100 mg daily;
Fluoxetine: from about 1 to about 80 mg, once/day; preferred, from about 10 to about 40 mg once/day; preferred for bulimia and obsessive-compulsive disease, from about 20 to about 80 mg once/day;
Duloxetine: from about 1 to about 160 mg once/day (or up to 80 mg twice daily); preferred, from about 5 to about 20 mg once/day;
40 Venlafaxine: from about 10 to about 150 mg once-thrice/day; preferred, from about 25 to about 125 mg thrice/day;
Milnacipran: from about 10 to about 100 mg once-twice/day; preferred, from about 25 to about 50 mg twice/day;
Citalopram: from about 5 to about 50 mg once/day; preferred, from about 10 to about 30 mg once/day;
Fluvoxamine: from about 20 to about 500 mg once/day; preferred, from about 50 to about 300 mg once/day;
Paroxetine: from about 20 to about 50 mg once/day; preferred, from about 20 to about 30 mg once/day.
45 Sertraline: from about 20 to about 500 mg once/day; preferred, from about 50 to about 200 mg once/day;

[0038] In more general terms, one would create a combination of the present invention by choosing a dosage of first and second component compounds according to the spirit of the above guideline.

[0039] Preferred ratios of olanzapine: fluoxetine by weight include:

50 1/5
6/25
12.5/25
25/50
55 17.5/50
25/75

[0040] The adjunctive therapy of the present invention is carried out by administering a first component together with

the second component in any manner which provides effective levels of the compounds in the body at the same time. All of the compounds concerned are orally available and are normally administered orally, and so oral administration of the adjunctive combination is preferred. They may be administered together, in a single dosage form, or may be administered separately.

5 [0041] However, oral administration is not the only route or even the only preferred route. For example, transdermal administration may be very desirable for patients who are forgetful or petulant about taking oral medicine. One of the drugs may be administered by one route, such as oral, and the others may be administered by the transdermal, percutaneous, intravenous, intramuscular, intranasal or intrarectal route, in particular circumstances. The route of administration may be varied in any way, limited by the physical properties of the drugs and the convenience of the patient

10 and the caregiver.

[0042] The adjunctive combination may be administered as a single pharmaceutical composition, and so pharmaceutical compositions incorporating both compounds are important embodiments of the present invention. Such compositions may take any physical form which is pharmaceutically acceptable, but orally usable pharmaceutical compositions are particularly preferred. Such adjunctive pharmaceutical compositions contain an effective amount of each of the compounds, which effective amount is related to the daily dose of the compounds to be administered. Each adjunctive dosage unit may contain the daily doses of all compounds, or may contain a fraction of the daily doses, such as one-third of the doses. Alternatively, each dosage unit may contain the entire dose of one of the compounds, and a fraction of the dose of the other compounds. In such case, the patient would daily take one of the combination dosage units, and one or more units containing only the other compounds. The amounts of each drug to be contained

20 in each dosage unit depends on the identity of the drugs chosen for the therapy, and other factors such as the indication for which the adjunctive therapy is being given.

[0043] The inert ingredients and manner of formulation of the adjunctive pharmaceutical compositions are conventional, except for the presence of the combination of the present invention. The usual methods of formulation used in pharmaceutical science may be used here. All of the usual types of compositions may be used, including tablets, chewable tablets, capsules, solutions, parenteral solutions, intranasal sprays or powders, troches, suppositories, transdermal patches and suspensions. In general, compositions contain from about 0.5% to about 50% of the compounds in total, depending on the desired doses and the type of composition to be used. The amount of the compounds, however, is best defined as the effective amount, that is, the amount of each compound which provides the desired dose to the patient in need of such treatment. The activity of the adjunctive combinations do not depend on the nature of the composition, so the compositions are chosen and formulated solely for convenience and economy. Any of the combinations may be formulated in any desired form of composition. Some discussion of different compositions will be provided, followed by some typical formulations.

[0044] Capsules are prepared by mixing the compound with a suitable diluent and filling the proper amount of the mixture in capsules. The usual diluents include inert powdered substances such as starch of many different kinds, powdered cellulose, especially crystalline and microcrystalline cellulose, sugars such as fructose, mannitol and sucrose, grain flours and similar edible powders.

[0045] Tablets are prepared by direct compression, by wet granulation, or by dry granulation. Their formulations usually incorporate diluents, binders, lubricants and disintegrators as well as the compound. Typical diluents include, for example, various types of starch, lactose, mannitol, kaolin, calcium phosphate or sulfate, inorganic salts such as sodium chloride and powdered sugar. Powdered cellulose derivatives are also useful. Typical tablet binders are substances such as starch, gelatin and sugars such as lactose, fructose, glucose and the like. Natural and synthetic gums are also convenient, including acacia, alginates, methylcellulose, polyvinylpyrrolidone and the like. Polyethylene glycol, ethylcellulose and waxes can also serve as binders.

[0046] A lubricant is necessary in a tablet formulation to prevent the tablet and punches from sticking in the die. The lubricant is chosen from such slippery solids as talc, magnesium and calcium stearate, stearic acid and hydrogenated vegetable oils.

[0047] Tablet disintegrators are substances which swell when wetted to break up the tablet and release the compound. They include starches, clays, celluloses, algins and gums. More particularly, corn and potato starches, methylcellulose, agar, bentonite, wood cellulose, powdered natural sponge, cation-exchange resins, alginic acid, guar gum, citrus pulp and carboxymethylcellulose, for example, may be used, as well as sodium lauryl sulfate.

[0048] Enteric formulations are often used to protect an active ingredient from the strongly acid contents of the stomach. Such formulations are created by coating a solid dosage form with a film of a polymer which is insoluble in acid environments, and soluble in basic environments. Exemplary films are cellulose acetate phthalate, polyvinyl acetate phthalate, hydroxypropyl methylcellulose phthalate and hydroxypropyl methylcellulose acetate succinate. It is preferred to formulate duloxetine and duloxetine-containing combinations as enteric compositions, and even more preferred to formulate them as enteric pellets.

[0049] A preferred duloxetine enteric formulation is a pellet formulation comprising a) a core consisting of duloxetine and a pharmaceutically acceptable excipient; b) an optional separating layer; c) an enteric layer comprising hydroxy-

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propylmethylcellulose acetate succinate (HPMCAS) and a pharmaceutically acceptable excipient; d) an optional finishing layer. This enteric formulation is described in U.S. Patent No. 5,508,276, herein incorporated by reference in its entirety.

[0050] Tablets are often coated with sugar as a flavor and sealant. The compounds may also be formulated as chewable tablets, by using large amounts of pleasant-tasting substances such as mannitol in the formulation, as is now well-established practice. Instantly dissolving tablet-like formulations are also now frequently used to assure that the patient consumes the dosage form, and to avoid the difficulty in swallowing solid objects that bothers some patients.

[0051] When it is desired to administer the combination as a suppository, the usual bases may be used. Cocoa butter is a traditional suppository base, which may be modified by addition of waxes to raise its melting point slightly. Water-miscible suppository bases comprising, particularly, polyethylene glycols of various molecular weights are in wide use, also.

[0052] Transdermal patches have become popular recently. Typically they comprise a resinous composition in which the drugs will dissolve, or partially dissolve, which is held in contact with the skin by a film which protects the composition. Many patents have appeared in the field recently. Other, more complicated patch compositions are also in use, particularly those having a membrane pierced with innumerable pores through which the drugs are pumped by osmotic action.

[0053] The following typical formulae are provided for the interest and information of the pharmaceutical scientist.

Formulation 1

[0054] Hard gelatin capsules are prepared using the following ingredients:

	Quantity (mg/capsule)
Olanzapine	25 mg
Fluoxetine, racemic, hydrochloride	20
Starch, dried	150
Magnesium stearate	10
Total	210 mg

Formulation 2

[0055] A tablet is prepared using the ingredients below:

	Quantity (mg/capsule)
Olanzapine	10
Fluoxetine, racemic, hydrochloride	10
Cellulose, microcrystalline	275
Silicon dioxide, fumed	10
Stearic acid	5
Total	310 mg

The components are blended and compressed to form tablets each weighing 465 mg.

Formulation 3

[0056] An aerosol solution is prepared containing the following components:

	Weight
Risperidone	5 mg
(+)-Duloxetine, hydrochloride	10
Ethanol	25.75
Propellant 22 (Chlorodifluoromethane)	60.00
Total	100.75 mg

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[0057] The active compound is mixed with ethanol and the mixture added to a portion of the propellant 22, cooled to -30°C and transferred to a filling device. The required amount is then fed to a stainless steel container and diluted with the remainder of the propellant. The valve units are then fitted to the container.

5 Formulation 4

[0058] Tablets, each containing 80 mg of active ingredient, are made as follows:

10	Sertindole	60 mg
	(+)-Duloxetine, hydrochloride	20 mg
	Starch	30 mg
	Microcrystalline cellulose	20 mg
	Polyvinylpyrrolidone (as 10% solution in water)	4 mg
15	Sodium carboxymethyl starch	4.5 mg
	Magnesium stearate	0.5 mg
	Talc	1 mg
	Total	<u>140 mg</u>

20 **[0059]** The active ingredient, starch and cellulose are passed through a No. 45 mesh U.S. sieve and mixed thoroughly. The aqueous solution containing polyvinylpyrrolidone is mixed with the resultant powder, and the mixture then is passed through a No. 14 mesh U.S. sieve. The granules so produced are dried at 50°C and passed through a No. 18 mesh U.S. Sieve. The sodium carboxymethyl starch, magnesium stearate and talc, previously passed through a No. 60 mesh U.S. sieve, are then added to the granules which, after mixing, are compressed on a tablet machine to yield tablets
25 each weighing 170 mg.

Formulation 5

30 **[0060]** Capsules, each containing 130 mg of active ingredient, are made as follows:

35	Quetiapine	70 mg
	Fluoxetine, racemic, hydrochloride	30 mg
	Starch	39 mg
	Microcrystalline cellulose	39 mg
	Magnesium stearate	2 mg
	Total	<u>180 mg</u>

40 **[0061]** The active ingredient, cellulose, starch, and magnesium stearate are blended, passed through a No. 45 mesh U.S. sieve, and filled into hard gelatin capsules in 250 mg quantities.

Formulation 6

45 **[0062]** Suppositories, each containing 45 mg of active ingredient, are made as follows:

50	Ziprasidone	75 mg
	(+)-Duloxetine, hydrochloride	5 mg
	Saturated fatty acid glycerides	2,000 mg
	Total	<u>2,080 mg</u>

[0063] The active ingredient is passed through a No. 60 mesh U.S. sieve and suspended in the saturated fatty acid glycerides previously melted using the minimum heat necessary. The mixture is then poured into a suppository mold of nominal 2 g capacity and allowed to cool.

55 Formulation 7

[0064] Suspensions, each containing 70 mg of active ingredient per 5 ml dose, are made as follows:

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Olanzapine	20 mg
Sertraline	100 mg
Sodium carboxymethyl cellulose	50 mg
Syrup	1.25 ml
Benzoic acid solution	0.10 ml
Flavor	q.v.
Color	q.v.
Purified water to total	5 ml

[0065] The active ingredient is passed through a No. 45 mesh U.S. sieve and mixed with the sodium carboxymethyl cellulose and syrup to form a smooth paste. The benzoic acid solution, flavor and color are diluted with a portion of the water and added, with stirring. Sufficient water is then added to produce the required volume.

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Formulation 8

[0066] An intravenous formulation may be prepared as follows:

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Olanzapine	20 mg
Paroxetine	25 mg
Isotonic saline	1,000 ml

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Benefit of the Invention

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[0067] The present invention provides the advantage of treatment of partial responding or refractory depression with the atypical antipsychotics without the concomitant weight gain typically observed with such treatment, conferring a marked and unexpected benefit on the patient. The present invention furthermore provides a potentiation of the increase in the concentration of dopamine and/or norepinephrine observed as an effect of administration of a first component compound, by administration of a second component compound.

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[0068] Moreover, the release of DA in the prefrontal cortex, either coupled with the antagonism of 5-HT₂ and/or 5-HT₃ receptors, would be expected to attenuate the disturbances in sexual function commonly associated with antidepressants such as the SSRIs. In addition, common SSRI-associated side effects such as nausea, vomiting, diarrhea, insomnia, weight change, headache, and or activation would be expected to be reduced in frequency/intensity based on the pharmacology of this novel combination.

Microdialysis assays of monoamines

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[0069] Sprague-Dawley rats (Harlan or Charles River) weighing 270-300 grams are surgically implanted with microdialysis probes under chloral hydrate/pentobarbital anesthesia (170 and 36 mg/kg i.p. in 30% propylene glycol, 14% ethanol) (Perry and Fuller, Effect of fluoxetine on serotonin and dopamine concentration in rat hypothalamus after administration of fluoxetine plus L-5-hydroxytryptophan, *Life Sci.*, 50, 1683-90 (1992)). A David Kopf stereotaxic instrument is used to implant the probe unilaterally in the hypothalamus at coordinates rostral -1.5 mm, lateral -1.3 mm, and ventral -9.0 mm (Paxinos and Watson, 1986). After a 48 hour recovery period, rats are placed in a large plastic bowl with a mounted liquid swivel system (CMA/120 system for freely moving animals, Bioanalytical Systems, West Lafayette, IN). Filtered artificial cerebrospinal fluid (CSF) (150 mM NaCl, 3.0 mM KCl, 1.7 mM CaCl₂, and 0.9 mM MgCl₂) is perfused through the probe at a rate of 1.0 ml/min. The output dialysate line is fitted to a tenport HPLC valve with a 20 ml loop. At the end of each 30 minute sampling period, dialysate collected in the loop is injected on an analytical column (Spherisorb 3 m ODS2, 2X150 mm, Keystone Scientific).

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[0070] The method used to measure monoamines is as described by Perry and Fuller (1992). Briefly, dialysate collected in the 20 ml loop is assayed for 5-HT, NE and DA. The 20 ml injection goes onto the column with a mobile phase which resolves NE, DA, and 5-HT: 75 mM potassium acetate, 0.5 mM ethylenediaminetetraacetic acid, 1.4 mM sodium octanesulfonic acid and 8% methanol, pH 4.9. The mobile phase for the amine column is delivered with a flow programmable pump at an initial flow rate of 0.2 ml/min increasing to 0.3 ml/min at 5 min then decreasing back to 0.2 ml/min at 26 min with a total run time of 30 min. Flow programming is used to elute the 5-HT within a 25 min time period. The electrochemical detector (EG&G, Model 400) for the amine column is set at a potential of 400 mV and a sensitivity of 0.2 nA/V. Basal levels are measured for at least 90 minutes prior to drug administration. The drugs are prepared in

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filtered deionized water (volume 0.25-0.3 ml) for administration at the desired doses.

Clinical Trials

5 [0071] The efficacy of the methods of the present invention in treating refractory depression or providing a more rapid onset of treatment of depression was shown in clinical trials. In one such study, an 8-week, double blind trial, 28 patients diagnosed with treatment-resistant major depression were randomized to one of three treatment arms: (1) fluoxetine (20-60 mg/day) and placebo; (2) olanzapine (5-20 mg/day) and placebo; or (3) fluoxetine plus olanzapine (20-60 mg/day and 5-20 mg/day, respectively). The efficacy of the treatment was monitored using the HAMD-21 (Ham-
10 ilton M. Journal of Neurology, Neurosurgery & Psychiatry. 1960;23:56-62, and Hamilton M. Development of a rating scale for primary depressive illness. British Journal of Social and Clinical Psychology. 1967;6:278-296); Montgomery-Asberg Depression Rating Scale (MADRS) (Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. British Journal of Psychiatry. 1979;134:382-389); and the Clinical Global Impression (CGI) - Severity of Depression rating scale (Guy, W. ECDEU Assessment Manual for Psychopharmacology. Revised ed. US Dept. of
15 Health, Education and Welfare, Bethesda, MD. 1976.) The olanzapine plus fluoxetine group experienced a greater improvement on both the HAMD-21 and MADRS total scores than either of the monotherapy groups. Superior rates of response (i.e., 50% or greater improvement from baseline) were also seen with this combination. Similar results were obtained using the CGI scale.

[0072] The antidepressant effect of olanzapine plus fluoxetine was evident within seven days of beginning the therapy. This is significantly earlier than is generally seen with a monotherapy using a serotonin uptake inhibitor alone, with no evidence of significant adverse interaction between the antipsychotic and the serotonin reuptake inhibitor.

Claims

- 25
1. A method for treating a patient suffering from or susceptible to treatment resistant major depression, comprising administering to said patient an effective amount of a first component which is an atypical antipsychotic, in combination with an effective amount of a second component which is a serotonin reuptake inhibitor.
 - 30 2. A method for treating a patient partially responding to treatment of major depression comprising administering to said patient an effective amount of a first component which is an atypical antipsychotic, in combination with an effective amount of a second component which is a serotonin reuptake inhibitor.
 - 35 3. A method for attenuating the adverse events associated with treating a patient suffering from or susceptible to treatment resistant major depression, or partially responding to treatment of major depression, comprising administering to said patient an effective amount of a first component which is an atypical antipsychotic, in combination with an effective amount of a second component which is a serotonin reuptake inhibitor.
 - 40 4. A method of any one of **Claims 1 to 3** where the first component is chosen from the group consisting of olanzapine, clozapine, risperidone, sertindole, quetiapine, and ziprasidone; and the second component is selected from the group consisting of fluoxetine, venlafaxine, citalopram, fluvoxamine, paroxetine, sertraline, milnacipran and duloxetine.
 - 45 5. A method of any one of **Claims 1 to 3** wherein the first component compound is olanzapine.
 6. A method of **Claim 4** wherein the second component compound is fluoxetine.
 7. A method of any one of **Claims 1 to 3** where administration of the compounds is oral.
 - 50 8. A method of **Claim 3** where the adverse event is selected from the group consisting of weight changes, sexual dysfunction, nausea, vomiting, diarrhea, insomnia, headache and activation.
 9. A method of any one of **Claims 1, 2, 3, 5 or 6** wherein the ratio of olanzapine to fluoxetine by weight is selected from the group consisting of 1/5, 6/25, 12.5/25, 25/50, 17.5/50 and 25/75.
 - 55 10. The use of an effective amount of a first component which is an atypical antipsychotic, in combination with an effective amount of a second component which is a serotonin reuptake inhibitor, for the manufacture of a medicament for the treatment of treatment resistant major depression.

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11. The use of an effective amount of a first component which is an atypical antipsychotic, in combination with an effective amount of a second component which is a serotonin reuptake inhibitor, for the manufacture of a medicament for the treatment of partial response to treatment of major depression.
- 5 12. The use of an effective amount of a first component which is an atypical antipsychotic, in combination with an effective amount of a second component which is a serotonin reuptake inhibitor, for the manufacture of a medicament for attenuating the adverse events associated with treatment of major depression, treatment resistant major depression or partial response to treatment of major depression.
- 10 13. A pharmaceutical composition adapted for the treatment of a patient suffering from or susceptible to treatment resistant major depression or partially responding to treatment for major depression, or attenuating the adverse effects associated with treatment of major depression, treatment resistant major depression or partial response to treatment of major depression, comprising as the active ingredients a combination of an atypical antipsychotic and a serotonin reuptake inhibitor.
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Señora Jefe,
DIVISIÓN DE NUEVAS CREACIONES
Superintendencia de Industria y Comercio
E. S. D.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No 06-021584- -00005-0000

Dep. 2020 NUECREACIONE
Eve: 378 FASENACIONALI
Folios: 106

Referencia : Expediente N° 06021584
Asunto : Oposición a la solicitud de patente de Invención titulada
"COMBINACION DE UN INHIBIDOR DE
RECAPTACION DE SEROTONINA Y LOXAPINA"
Solicitante : H LUNDBECK A/S.
Opositora : PROCAPS S.A.

Publicada en la Gaceta de la Propiedad Industrial
N° 580 del 28 de septiembre de 2007

Yo, **ELIANA ISAURA MORENO BOHORQUEZ**, abogada en ejercicio, identificada como aparece al pie de su firma, con tarjeta profesional No. 83823 del Consejo Superior de la Judicatura, en mi condición de apoderada de la sociedad **PROCAPS S.A.** conformada bajo las leyes de la República de Colombia y domiciliada en la ciudad de Barranquilla, Colombia, atentamente manifiesto que estando dentro del término de ley y por orden expresa de mi representada, presento oposición a la concesión del registro de la Patente de Invención titulada "**COMBINACION DE UN INHIBIDOR DE RECAPTACION DE SEROTONINA Y LOXAPINA**", cuyo titular es **H LUNDBECK A/S**, y pido a Usted declarar fundada esta oposición y en consecuencia negar el registro de la patente solicitada.

1. INTERÉS PARA ACTUAR

Conforme a lo dispuesto en el artículo 42 de la Decisión 486 de 2000 de la CAN, estando dentro del término estipulado por la ley, manifiesto el legítimo interés de nuestra representada para oponerse al registro de la patente de la referencia, atendiendo a que la solicitud pretendida no cumple con los requisitos dispuestos en la ley como se analizará más adelante y de ser concedida afectaría directamente la comercialización de algunos productos de mi representada, que contienen, en particular inhibidores de Serotonina y Loxapina. Por lo tanto, solicito respetuosamente a ese Despacho se sirva tener en cuenta la presente oposición dentro del trámite administrativo que se surte en esta Superintendencia.

2. FUNDAMENTOS DE HECHOS

2.1. La solicitud objeto de la presente fue presentada el 3 de marzo de 2006, reivindicando prioridad bajo las solicitudes DK20030001270 del 20030904; y, US20030500809P del 20030904, y fue publicada en Colombia, en la Gaceta de la Propiedad Industrial N° 580 del 28 de septiembre de 2007 página 431 y N° publicación 419, cuya publicación internacional corresponde a la WO2005023243 del 2005-03-17.

2.2. La solicitud colombiana **06-021584** objeto de la presente oposición, se refiere a una composición farmacéutica que comprende loxapina o una sal farmacéuticamente aceptable del mismo y un compuesto, el cual es inhibidor de recaptación de serotonina, el cual provoca una elevación en la concentración de serotonina extracelular, la cual opcionalmente presenta portadores o diluyentes

farmacéuticamente aceptables, donde el inhibidor de recaptación de serotonina se selecciona de citalopram, escitalopram, fluoxetina, sertralina, paroxetina, fluvoxamina, venlafaxina, dapoxetina, nefazodona, imipramina, femoxetina y clomipramina, en donde el inhibidor de recaptación de serotonina es un inhibidor selectivo de recaptación de serotonina, la cual está adaptada para administración simultánea de los ingredientes activos, en donde los ingredientes activos están contenidos en la misma forma de dosificación unitaria, en donde está adaptada para administración secuencial de los ingredientes activos.

2.3. Ahora bien, con base en el artículo 14 de la Decisión 486 de la CAN consagra lo siguiente: *“Los países miembros otorgarán patentes para las invenciones, sean de producto o procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial”*. Así las cosas, las invenciones objeto de patente deben ser nuevas y tener nivel inventivo. Bien, pues antes de la fecha de prioridad de esta solicitud se encuentran los siguientes documentos que afecta la patentabilidad de la presente solicitud:

- D1: WO0151041 publicada el 19 de julio de 2001.
- D2: US2002151543 publicada el 17 de octubre de 2002.
- D3: US2003130266 publicada el 10 de julio de 2003.
- D4: EP0958824 publicada el 24 de noviembre de 1999.

2.4. Ahora bien, el documento D1, particularmente revela una composición farmacéutica que comprende una forma osmótica de liberación controlada que contiene venlafaxina en el núcleo en combinación con un agente antipsicótico de rápida liberación en la cubierta. Esta forma, según el documento D1, es útil para el

tratamiento de la ansiedad, de depresión o psicosis. Con base en las reivindicaciones, el documento D1 revela con anterioridad una forma osmótica para la entrega de venlafaxina y un agente antipsicótico comprendiendo: un núcleo que comprende una cantidad terapéuticamente eficaz de VFX y al menos un agente osmótico u osmopolímero; una membrana semipermeable que rodea el núcleo; y una cubierta externa que comprende una cantidad terapéuticamente eficaz de un agente antipsicótico; en el que el núcleo proporciona una liberación controlada de VFX, y al menos el 80 % del VFX es liberado dentro de 13 horas después de que la exposición del dispositivo osmótico a una solución acuosa, y la cubierta proporciona una rápida liberación del agente antipsicótico, y al menos el 75 % del agente antipsicótico es liberado dentro de 1 hora después de la exposición de la forma osmótica a una solución acuosa. Así, las cosas, la presente solicitud no es novedosa pues lo revelado ya se encontraba en el estado de la técnica, particularmente en el documento D1.

2.5. Por su parte, el documento D2, revela una composición farmacéutica que comprende loxapina y (R)-fluoxetina para el tratamiento de la psicosis. Particularmente, este documento ya evidencia estudios y soluciones similares a la propuesta en la presente solicitud objeto de oposición, tal como el indicado en el párrafo 0039, que revela las enfermedades o los trastornos pueden ser tratados o prevenidos usando la R (-) fluoxetina y una benzodiazepina. En las reivindicaciones, este documento D2 revela un método para tratar una enfermedad psicótica o psiquiátrica en un mamífero que comprende la administración de una cantidad eficaz de R (-) fluoxetine o una sal farmacéuticamente aceptable, considerablemente sin su S (+) el estereoisómero, y una cantidad eficaz de un compuesto biológicamente activo tricíclico antipsicótico. Por lo tanto, este documento objeto de oposición a la luz del documento D2 carece evidentemente de NOVEDAD.

2.6. Ahora bien, el documento D3, también ofrece una solución similar a la aquí propuesta dado que se revela con anterioridad una combinación farmacéutica de un inhibidor de SSR y un antagonista receptor de serotonina. En esta anterioridad se revelan varios ejemplos que ello, que incluyen una cantidad de loxapina. De hecho en la cláusula 13, revela un método de tratamiento en trastornos respiratorios relacionados con el sueño que comprende administrar a un paciente una cantidad eficaz de al menos un antagonista receptor de serotonina en su base libre o en su forma de cuaternaria seleccionada del grupo que consiste en zatosetrona, tropisetrona, dolasetrona, hidrodolasetrona, mezcaltina, oxetorona, homoclorciclizina, perlapina, loxapina, olanzapina, calpromazina, haloperidol, r (+) ondansetrona, cisaprida, norcisaprida, (+) cisaprida, (-) cisaprida, (+) norcisaprida, (-) norcisaprida, desmetilolanzapina, 2-hidroximetilolanzapina, 1-3-oxime (2-fluorofenil) (4-hidroxiaminoetil)-prop-2-en-1-one-O-(2-dimetilaminoetil); y en su forma de cuaternaria seleccionada del grupo que consiste en ondansetrona, ketanserina, risperidona, cyproheptadina, clozapina, methysergida, granisetrona, mianserina, ritanserina, cinanserina, LY-53,857, metergolina, LY-278,584, methiothepin, p-NPPL, YAYA 190, piperazine, SB-206553, SDZ-205,557, 3-tropanil-indole-3-20 carboxilato, y 3-tropanil-indol-3-carboxilato metiodida; y mezclas de los mismo; y una cantidad eficaz de un inhibidor selectivo serotonina. Por lo tanto, a los ojos de este documento D3, la presente solicitud también carece evidentemente de novedad.

2.7. El documento D4, revela por su parte una composición farmacéutica adaptada para el tratamiento de un paciente que sufre de depresión que incluye ingredientes activos en una combinación de antipsicóticos y un inhibidor de nueva respuesta serotonina. Como tal, las reivindicaciones de este documento D4, revelan con anterioridad un método para tratar un paciente que sufre de depresión que comprende administrar al paciente una cantidad eficaz de un primer componente

de un antipsicótico atípico, en la combinación con una cantidad eficaz de un segundo componente que es un inhibidor de serotonina. De esta manera, este documento objeto de oposición a la luz del documento D4 también carece evidentemente de NOVEDAD.

2.8. En consecuencia y de acuerdo a lo descrito anteriormente, se deriva que la solicitud colombiana **06-021584** no puede pretender un monopolio por patente toda vez que lo que pretende no cumple con los requisitos necesarios para su protección.

2.9. Que por consiguiente, respecto a la solicitud pretendida se tiene que:

2.9.1. **CARECE DE NOVEDAD**: Según la decisión 486 de la Comunidad Andina de Naciones, Artículo 16.- *“Una invención se considerará nueva cuando no está comprendida en el estado de la técnica. El estado de la técnica comprenderá todo lo que haya sido accesible al público por una descripción escrita u oral, utilización, comercialización o cualquier otro medio antes de la fecha de presentación de la solicitud de patente o, en su caso, de la prioridad reconocida.”* A la fecha de prioridad, 4 de septiembre de 2003 ya era conocido, pues como se demostró, era parte del arte anterior con base en los documentos D1, D2, D3 y D4 una composición farmacéutica que comprende loxapina o una sal farmacéuticamente aceptable del mismo y un compuesto, el cual es inhibidor de recaptación de serotonina, la cual provoca una elevación en la concentración de serotonina extracelular, la cual opcionalmente presenta portadores o diluyentes farmacéuticamente aceptables, en donde los ingredientes activos están contenidos en la misma forma de dosificación unitaria, en donde está adaptada para administración secuencial de los ingredientes activos, sobre el cual busca protección en el capítulo reivindicatorio.

2.10. Dado lo anterior, es posible deducir que la solicitud y lo reivindicado no es objeto de patentabilidad pues es contrario a lo que dicta la Decisión 486 de la Comunidad Andina de Naciones, Artículo 14.- *“Los Países Miembros otorgarán*

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patentes para las invenciones, sean de producto o de procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial.”. La solicitud pretendida no cumple con los requisitos de patentabilidad, particularmente la NOVEDAD.

2.11. Por todo lo anterior, atentamente solicito a usted que se sirva declarar fundada la presente oposición y negar el registro Patente de invención denominada **“COMBINACION DE UN INHIBIDOR DE RECAPTACION DE SEROTONINA Y LOXAPINA”**, cuyo titular es **H LUNDBECK A/S**, solicitud Colombiana que apareció publicada en la Gaceta de la Propiedad Industrial N° 580.

3. PRUEBAS

De conformidad con lo dispuesto por las normas vigentes, solicito a usted tener como prueba en este asunto los siguientes:

- D1: WO0151041 publicada el 19 de julio de 2001.
- D2: US2002151543 publicada el 17 de octubre de 2002.
- D3: US2003130266 publicada el 10 de julio de 2003.
- D4: EP0958824 publicada el 24 de noviembre de 1999.

4. FUNDAMENTO DE DERECHO

Fundamento esta observación en las normas legales siguientes:

- 4.1. Numeral 1 del artículo 586 del Código de Comercio.
- 4.2. Artículo 42 de la Decisión 486 de la Comisión del Acuerdo de Cartagena.
- 4.3. En las demás normas concordantes.

5. ANEXOS

Para los efectos correspondientes anexo al presente escrito los siguientes documentos:

1. Poder para actuar en el presente.
2. Documento que acredita al representante legal de PROCAPS S.A.
3. Recibo de caja del respectivo pago de tasa.
4. Copias de los documentos:
 - D1: WO0151041 publicada el 19 de julio de 2001.
 - D2: US2002151543 publicada el 17 de octubre de 2002.
 - D3: US2003130266 publicada el 10 de julio de 2003.
 - D4: EP0958824 publicada el 24 de noviembre de 1999.

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6. NOTIFICACIONES

Para efectos de notificaciones que por disposición del artículo 50 del Decreto 01 de 1984 debe hacer su Despacho, informo que mi representada y la suscrita recibiremos notificaciones en la Secretaría de su Despacho o en mis oficinas situadas en la Carrera 13 N° 119-95, Of. 104 de esta ciudad de Bogotá.

Señor Superintendente,

ELIANA ISAURA MORENO BOHORQUEZ

C.C. 51'975.664 de Bogotá

T.P.A. 83823 del C.S. de la J.