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Principia Marsupia

"Descifrar lo que está delante de nuestros ojos requiere una lucha constante" Orwell

Cómo las farmacéuticas engañan a médicos y pacientes

Publicado el 24 de septiembre de 2012

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El escándalo de la reboxetina debería haber encendido todas las alarmas. Aprobada en muchos países europeos desde finales de los 90, la reboxetina es el principio activo de un fármaco para la depresión clínica.

En año 2010, un grupo de investigadores alemanes publicó en el British Medical Journal un estudio que demostraba que **no sólo el medicamento era inefectivo, sino que, además, la compañía farmacéutica había ocultado a la comunidad médica aquellos tests que le eran desfavorables.** De 7 ensayos clínicos contra placebo, 6 mostraban que la reboxetina no era más eficaz que el placebo. Ninguno de esos 6 estudios fue publicado en revistas científicas. Además, en los ensayos clínicos contra otros antidepresivos, la compañía farmacéutica había eliminado tres cuartas partes de los datos.

(Nota: el artículo del British Medical Journal que destapó el caso es gratuito y podéis leerlo aquí).

Inexplicablemente, en España la reboxetina sigue siendo comercializada por Pfizer bajo los nombres "Norebox" e "Irenor" (números de registro 61969 y 63157 en la Agencia Española del Medicamento). La agencia federal que supervisa los fármacos en los EEUU (conocida por sus siglas, FDA) nunca aprobó la reboxetina por falta de eficacia probada.

Pfizer no es la única compañía envuelta en un escándalo de ocultación de datos científicos. En Febrero de 2010, **el Senado de EEUU publicó un informe donde se describe cómo la farmacéutica GlaxoSmithKline (GSK) no sólo mintió sobre los riegos cardiovasculares de uno de sus medicamentos contra la diabetes sino que además trató de silenciar a los científicos que los advirtieron.** La FDA calcula que este fármaco produjo 83.000 infartos entre los años 1999 y 2007. Hace unos meses, GSK decidió declarase culpable ante los tribunales norteamericanos.

El caso se remonta a 1999. En varias conferencias científicas celebradas aquel año, el Dr. John Buse, profesor en la Universidad de Carolina del Norte-Chapel Hill, comenzó a advertir sobre los posibles riesgos de la rosiglitazona, un medicamento que suponía miles de millones de ingresos para GSK. Tachi Yamada, entonces director de investigación de GSK, envió una serie de emails intimidatorios a Buse, quien decidió cesar sus críticas.

Ben Goldacre, doctor en Medicina e investigador en la Universidad de Oxford, explora las razones de algunos de estos fraudes en un libro que se publicará esta semana en el Reino Unido. Según Goldacre, la regulación de la industria farmacéutica es todavía deficiente. Por ejemplo, las compañías farmacéuticas no están obligadas a publicar todos los ensayos clínicos que realizan y por lo tanto, los que se hacen públicos son casi siempre favorables a sus intereses. Es también una práctica habitual que, cuando investigadores universitarios aceptan financiación de una farmacéutica, se les haga firmar un contrato por el cual no pueden publicar ningún resultado sin el permiso de la compañía. Las farmacéuticas financian además numerosas revistas y conferencias médicas.

Al igual que con la crisis bancaria, abandonar una industria multibillonaria a las fuerzas del mercado, *sin una regulación adecuada,* puede tener consecuencias nefastas para todos.

Esta entrada fue publicada en Ciencia y etiquetada agencia, española, farmacéuticas, fda, gsk, industria, medicamento, medicamentos, médicos, reboxetina, regulación, rosiglitazona por alberto. Guarda enlace permanente.

74 pensamientos en "Cómo las farmacéuticas engañan a médicos y pacientes"

1. Blog Economía Española en 24 de septiembre de 2012 en 08:24 dijo:

   Industrias multiBILLONARIAS, sí señor.

   Responder ↓
2. Pingback: Cómo las farmacéuticas engañan a médicos y pacientes – Principia Marsupia | ObservatorisalutPV
3. Gusanita Diminuta en 24 de septiembre de 2012 en 09:07 dijo:

   Pfizer también ocultó datos sobre la paroxetina y a saber qué más… Hay un documental de la BBC sobre ello.

   Responder ↓
   - Andrés en 24 de septiembre de 2012 en 09:50 dijo:

Gusanita, si tienes más información sobre lo que dices de la paroxetina, te la agradecía, muchas gracias.

Responder ↓

- Sergio-Javier en 24 de septiembre de 2012 en 10:39 dijo:

  Recuerdo haber visto ese documental sobre la paroxetina (Seroxat,…) hace años, y si no recuerdo mal, adevertía de que con un uso continuado, producía una dependencia brutal, y cuando los pacientes tenían que dejar de tomarlo lo pasaban fatal. Que alguien me corrija si me equivoco, ya digo que lo vi hace mucho.

- pablo en 24 de septiembre de 2012 en 15:56 dijo:

  Andrés, yo también estoy buscando información sobre la paroxetina… también de la venlafaxina. emm…si quieres conocer un historia muy dura, una historia…digamos, dejémoslo en muy dura. Es la mía, con la paroxetina…hace 10 meses que la deje, y aún todavía sufro repercusiones y efectos secundarios. Pero hay que saber luchar, y yo estoy abierto a contar a todo el mundo mi experiencia. Ojalá pudiera denunciar a las farmaceuticas… no sé como, y no es por beneficio económico, sino por orgullos, por esa ira e impotencia de pensar que las que se suponía me tenian que curar…me hayan jodido más. en fin dejo aquí mi e-mail para el que quiera saber más de mí: pablopariciooncins@gmail.com

- Alguien que cree en la ciencia en 25 de septiembre de 2012 en 20:02 dijo:

  La verdad es que el artículo es bastante lamentable. Estáis poniendo en duda la credibilidad de la profesionales de la medicina. La medicina se basa en la evidencia, y aquí vosotros os basáis en la rumoro logia .

  Responder ↓

  - María Paz Barriales Soto en 26 de septiembre de 2012 en 01:06 dijo:

    yo no creo, lo primero en la medicina, creo que todo se basa en el dinero, no me creo que en poco tiempo hayan dsido capaces de sacar una cura para el sida y no hayan descubierto nada para el cancer, lo que pasa es que no interesa, los tratamientos para el cancer dejan mucho dinero, y no interesa acabar con él, si el sida no hubiese sido contagioso hubiera pasado lo mismo, pero aquí era más problemático, en este mundo lo que importa es la pasta y no la vida de las personas, no creo en los médicos, pero no por ellos sino porque les tienen tan engañados como a todos los demás, las farmaceuticas son las que mandan y cuando surge algún medicamento que parece quer puede surgir efecto sobre el cancer, terrible enfermedad, tardan bastante poco en desmentir y en retirar dicho medicamento, nunca voy al médico me trato yo con medicina natural de herbolario, de momento todo me va bien y el día que me vaya mal, pués a criar malvas, pero procuraré que ellos no me pongan la mano encima, porque conozco varios casos de personas que estaban bien, le detectaron la enfermedad por casualidad, y en cuanto les empezaron a tratar, cayeron en picado, entre ellos mi padre, no quiero nada de la medicina que se practica hoy en día

4. María en 24 de septiembre de 2012 en 09:11 dijo:

   De acuerdo en todo, pero no estaría mal incluir en la crítica que hay que meter en el mismo saco a la farmaceútica homeopática, que desde el principio la ciencia ya ha demostrado

claramente que engaña a quienes les compra.

Responder ↓

- cesar en 24 de septiembre de 2012 en 10:34 dijo:

  mi ultimo trabajo en España fue de Director técnico en una farmaceutica que comercializaba homeopáticos. Con un buen sueldo. Los estudios no daban resultados y cuando se lo dije al dueño de la empresa me echaron, por pesimista y no defender la imagen de la empresa,. Yo contento de haber defendido la verdad. .Tienen además expedientes abiertos por utilizar corticoides en la formulación. Las farmaceuticas son mafias, y son el caso más ilustrativo de lo que ocurre si no hay un regulador que las frene . Bueno quizás tenemos ahora el ejempo de los bancos …

  Responder ↓
- boss en 24 de septiembre de 2012 en 10:40 dijo:

  Con un atenuante: el agua y las pastillitas no perjudican la salud de nadie.

  Responder ↓
  - ateo666666 en 24 de septiembre de 2012 en 11:15 dijo:

    ¿qué me dices del bolsillo?. Porque las pastillas de agua y azucar a 10-20 euros me parece un poco caro. Y si además induce a dejar un tratamiento efectivo pues entonces también mata. http://diario-de-un-ateo.blogspot.com.es/2011/10/homeopatia-y-multinacionales.html
    - Naidetres en 24 de septiembre de 2012 en 13:00 dijo:

      No es cierto, si un paciente abandona un tratamiento cuya efectividad está basada en la evidencia por esas pastillitas de sacarina…
- Naidetres en 24 de septiembre de 2012 en 12:58 dijo:

  Sí, sí, por supuesto, y más aún, puesto que nunca ha demostrado científicamente resultados más allá del placebo. Sobre todo eso habla Goldacre en su libro imprescindible: Mala ciencia.

  Responder ↓
- Tanit en 25 de septiembre de 2012 en 00:05 dijo:

  Hay que saber como funciona la homeopatía. todo es ciencia. no digo que la industria no juegue con los pacientes, pero cuidado, la homeopatía no hará daño a nadie, simplemente hay que saber como funciona y por qué a veces no se perciben resultados.

  Responder ↓
- eva canizal en 25 de septiembre de 2012 en 12:37 dijo:

  No estoy de acuerdo contigo, la homeopatía está demostrado que funciona para determinadas personas, de hecho, alemanes y franceses son muy buenos pacientes, Va muy bien para determinadas enfermedades, al igual que las medicaciones tradicionales, solo que con menos efectos secundarios, eso sí carisiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiisima.

  Responder ↓

5. Gusanita Diminuta en 24 de septiembre de 2012 en 09:11 dijo:

   Ay no! Seroxat es de GSK: http://news.bbc.co.uk/2/hi/programmes/panorama/2310197.stm

Responder ↓

6. Anónimo en 24 de septiembre de 2012 en 09:11 dijo:

   No cabe la menor duda de que las compañías farmacéuticas engañan a los ciudadanos, afectando así gravemente su derecho a la salud y su economía, pero su relación con los médicos y con las autoridades encargadas de autorizar sus productos no puede decirse que sea de engaño en la mayor parte de las ocasiones sino de colaboración en un modelo de crimen organizado que antepone el lucro a los derechos humanos. Los sobornos al personal sanitario son más que notorios y la corrupción de puertas giratorias entre las compañías farmacéuticas y los responsables sanitarios se viene denunciando con la más absoluta impunidad.

   Responder ↓

   - Miguel Jara en 24 de septiembre de 2012 en 09:17 dijo:

     La mayor parte del marketing de buena parte de las farmacéuticas es ilegal, mirad lo que escribe un fiscal en España http://www.migueljara.com/2012/09/05/la-mayor-parte-del-marketing-de-las-farmaceuticas-a-los-medicos-es-ilegal/

     Responder ↓

7. Miguel Jara en 24 de septiembre de 2012 en 09:14 dijo:

   Al hilo de esto se ha producido la segunda sentencia en el mundo contra Bayer por ocultar datos de un medicamento y matar a más de cien personas, sólo en España, en el resto del mundo ¿cuantas? http://www.migueljara.com/2012/09/21/la-victoria-del-david-flavio-contra-el-goliat-bayer/

   Responder ↓

8. Andrés en 24 de septiembre de 2012 en 09:23 dijo:

   Gusanita o cualquiera que sepa ¿ me puedes ampliar información sobre lo que dices de la paroxetina? La tomo, y me gustaría saber más, muchas gracias por adelantado.

   Responder ↓

9. Luis en 24 de septiembre de 2012 en 09:25 dijo:

   Hola Alberto,lo primero enhorabuena por el blog, y por conseguir llevar la ciencia a primera lìnea del debate de vez en cuando.
   No dudo que todo esto que escribes sea verdad, pero caemos en el riesgo de la generalizaciòn. Somos cientìficos y como tales estamos obligados (sòlo éticamente, para bien y para mal) a la crìtica (y la autocrìtica), y a la denuncia de las malas pràcticas. Pero segùn està el percal, sembrar màs dudas sobre la ciencia y sus procedimientos aumentarà la peligrosa tendencia anti-cientìfica y empujarà a màs y màs gente hacia ese pantanoso terreno de la pseudociencia. Porque la gente busca verdades absolutas y cada dìa las encuentra màs en su “chamàn/curandero/ecobioholìstico” y menos en la Medicina y en la Ciencia (en su versiòn mal llamémosla “oficial”). Por esto, a esa responsabilidad autoimpuesta de la denuncia de malas artes en nuestro campo va sumada la responsabilidad de no hacer del caso concreto una generalidad, y por ello entiendo que cada crìtica deberìa ir acompañada de un reconocimiento de lo que sì funciona del sistema.
   De otra manera estaremos siendo còmplices de una situaciòn cada vez màs frecuente: el rechazo, por desconfianza, de cada vez màs gente a vacunas, tratamientos y fàrmacos perfectamente eficaces y necesarios para la salud personal y pùblica.
   Un saludo y suerte.

   Responder ↓

10. Dansk en 24 de septiembre de 2012 en 09:26 dijo:

Como siempre, generalizar tan tajantemente es pura demagogia. Hay empresas que no se toman en serio su trabajo, pero yo trabajo en una pequeña empresa farmacéutica y cuidamos muchísimo la producción y testamos enormemente cada producto antes de comercializarlo. Hay que atacar a estas empresas que han puesto en peligro a sus pacientes, pero no se puede arremeter tan a la ligera contra todo un sector.

Responder ↓

11. Mari Delfino (@TangaraUK) en 24 de septiembre de 2012 en 09:34 dijo:

    Marsupia, esta información es la que aparece en el libro Bad Pharma de Ben Goldacre, recién publicado en Reino Unido. Si te has inspirado en el trabajo del Dr, Goldacre, sería apropiado que lo menciones.

    Responder ↓

12. Anónimo en 24 de septiembre de 2012 en 09:58 dijo:

    Mientras los ensayos clinicos los sigan diseñando , financiando y controlando las empresas farmaceuticas que comercializarán el fármaco en cuestión será muy difícil para las agencias (FDA y otras) controlar dichos ensayos clínicos y laua resultados.

    Responder ↓

13. Bern en 24 de septiembre de 2012 en 10:17 dijo:

    Pues entro los lectores de “Público” hay un porcentaje importante que está convencido de que los estudios a que se someten los fármacos antes de lanzarlos al mercado son de una perfección científica total, y cada vez que yo he puesto en duda esa supuesta perfección me han llovido las críticas e incluso los insultos. Estaría bien que algunos destacados cientificistas lectores de este medio tomaran buena nota de esta noticia.

    Responder ↓

14. Julio en 24 de septiembre de 2012 en 10:31 dijo:

    Hola Luis. Según he entendido yo, del artículo, la ciencia (así en abstracto), no sólo no ha errado en estos casos, sinoque es la responsable directa de que salgan a la luz:

    “un grupo de investigadores alemanes publicó en el British Medical Journal un estudio que demostraba que no sólo el medicamento era inefectivo, sino que, además, la compañía farmacéutica había ocultado a la comunidad médica aquellos tests que le eran desfavorables”

    Es decir, la ciencia y su método, incluso aplicada por la propia Industria, da una información válida en todos los casos. Lo que realmente queda en cuestión es la credibilidad de esa Industria, que se permite ocultar los resultados que no le interesa.

    Este tipo de noticias debería animar fuertemente a favor de la ciencia como fuente libre y pública de conocimiento.

    Responder ↓

15. Anónimo en 24 de septiembre de 2012 en 10:32 dijo:

    Afortunadamente ahora cada vez se utiliza más el metanálisis (agrupación de varios ensayos clínicos similares) con lo que se consigue un tamaño muestral muy grande y por tanto son mucho más fiables.

    Responder ↓

16. Anónimo en 24 de septiembre de 2012 en 10:41 dijo:

    Que la crisis va mucho más ayá de la ecomomía lo prueba el que ya no se pueda uno fiar de los políticos, jueces, curas, medios de comunicación, etc, etc,……..

Responder ↓

17. Daza en 24 de septiembre de 2012 en 10:46 dijo:

    Yo estaba por la legalización de las drogas, pero visto lo visto casi que prefiero a mi camello de toda la vida: Lo más que ha llegado a hecer es venderme polvos de talco a 60 pavos el gramo, pero incluso así, tiene la deferencia de avisarte de que “esta vez no es muy buena”.

    Responder ↓

18. JOSE ORTEGA MENDEZ en 24 de septiembre de 2012 en 10:58 dijo:

    Population Council, (en español, Consejo de Población) es una organización internacional sin ánimo de lucro, fundada en secreto por John Davison Rockefeller III. El consejo lleva a cabo investigaciones biomédicas y de ciencias sociales. Un tercio de sus investigaciones se involucran en investigar el VIH y el SIDA.

    Otras de sus áreas tienen que ver con la salud reproductiva. Entre sus planes cuenta con la disminución drástica de la población mundial desde 6.000 millones de hoy a 500 millones mañana. También dirige investigaciones sobre la pobreza, la juventud y “estudios de género”. Ayudó a la creación de Norplant un implante usado como método anticonceptivo subdérmico desarrollado en 1983. En la actualidad tienen la licencia de Mirena un método anticonceptivo intrauterino. También lanzan la revista Population and Development Review que discute la relación entre población y socio-economía. Creada en 1952, con importantes recursos de Rockefeller Brothers Fund, su primer director Frederick Osborn, fundador del Pioneer Fund (Fondo Pionero) tiene un pasado “eugenista”. La organización es independiente de cualquier gobierno. Entre sus miembros cuenta con diversos medios, de la biomedicina, de las finanzas internacionales, entes gubernamentales, medios de comunicación, filántropos, etc.

    Responder ↓

19. Abel Ruiz en 24 de septiembre de 2012 en 11:02 dijo:

    Al margen de la fiabilidad de los ensayos, las compañías farmacéuticas vienen demostrando cada dos por tres que su único interés es reinventar la rueda una y otra vez, a base de patentar nuevos principios activos que puedan cobrar a precios astronómicos. Todo lo demás sencillamente no interesa.

    Una demostración más de lo poco que les importa perfeccionar y mejorar lo existente la tenemos en su absoluta desidia ante la necesidad imperiosa de ahondar en la posibilidad de que los anti-inflamatorios pudieran prevenir una enfermedad tan seria como el Alzheimer.

    Pero, ¿cómo podría interesarles algo así? ¿Que un principio activo como el Ibuprofeno, barato y testado a más no poder, pudiera tener un papel importante en algo así cuando ellos, de forma paralela, están invirtiendo millonadas en otro principio activo para combatir las “placas” que otra parte de la comunidad científica piensa que podrían ser la causa de la enfermedad?

    ¿Por qué no investigar las dos vías a la vez…? Sencillo: porque no quieren ni oír hablar de la primera, aunque pudiera ser la mejor para nosotros.

    Otro ejemplo más de cómo el dinero ha venido a sustituir a la razón y la humanidad.

    Responder ↓

    - kanguelo en 24 de septiembre de 2012 en 12:41 dijo:

      Hola, Abel, me interesa eso que dices del ibuprofeno en relación con el alzheimer. Si no te he entendido mal ¿el ibuprofeno podría prevenir el alzheimer?
      Gracias y un saludo.

Responder ↓

- Abel Ruiz en 24 de septiembre de 2012 en 14:29 dijo:

  Podría ser. Lo vi en "La Noche Temática" el otro día.

  A un científico que lo investiga (no recuerdo el nombre) le llamó la atención que apenas hubiera casos de Alzheimer entre la gente de edad avanzada y con riesgo de padecerlo, que a su vez tuvieron y tienen reumatismo (gente que toma bastantes anti-inflamatorios para lidiar con el dolor).

  Total, que se puso a contrastarlo para comprobar si era casualidad y pudo confirmar con datos estadísticos que sí que había una correlación directa. Pero claro, sólo es una persona (o un puñado) con una teoría que, por muy prometedora que sea, no puede realizar los ensayos clínicos enfocados a seguir profundizando en esta posibilidad. Y, como es lógico, a ninguna empresa farmacéutica le interesa invertir dinero en algo que sólo añadiría una ventaja más a un principio activo que no pueden patentar porque ya es un genérico.

  En resumen, que nadie puede decirte ahora "-Toma anti-inflamatorios para prevenir el Alzheimer." con total autoridad científica. Pero también es posible que nadie pueda llegar a constatarlo porque no reportará beneficios económicos a nadie.

  Ahora bien, a título personal yo ya tomaba de vez en cuando Ibuprofeno por los dolores de cabeza… De modo que lo seguiré haciendo con mayor confianza aún si cabe… Me parece demasiado prometedor e inofensivo como para despreciar las posibles ventajas.

- chabi en 25 de septiembre de 2012 en 11:00 dijo:

  ¿Por qué tiene que investigar esto la industria farmaceutica? Es un ejemplo perfecto del trabajo que debe hacer la investigación pública, un genérico y médicos de familia aportando datos durante años, no es precisamente el viaje a Marte coño.

  Responder ↓

20. Fco en 24 de septiembre de 2012 en 11:15 dijo:

    Febrero se escribe con minúscula, en castellano es nombre común.

    Responder ↓

    - fabricio en 24 de septiembre de 2012 en 18:24 dijo:

      Listillo.

      Responder ↓

21. Alex en 24 de septiembre de 2012 en 11:20 dijo:

    "Que tu alimento sea tu medicina, y que tu medicina sea tu alimento" Y pasar de tantas pastillas, porque el dinero supera a ser profesional y objetivo.

    Responder ↓

22. ateo666666 en 24 de septiembre de 2012 en 11:22 dijo:

    Lo importante no es si de vez en cuando las farmaceúticas engañan, eso se arregla investigando y sancionando a los culpables. Nunca hay un colectivo perfecto al completo. Lo verdaderamente grave en la sanidad es que hay sectores enteros: homeopatía, pseudomedicina, curanderos, etc que estafan sin ningún control a millones de personas y que

mueven en el mundo miles de millones de euros en sus vergonzosos engaños. Ojalá todos estos timadores estuvieran siendo investigados tan exhaustivamente como lo son los medicamentos de la medicina científica porque en ese caso los juzgados de todo el mundo estarían saturados de trabajo y las cárceles del planeta llenas de estos impresentables estafadores que juegan con las esperanzas de los más ignorantes. http://diario-de-un-ateo.blogspot.com.es/2011/12/el-timo-de-las-terapias-naturales.html

Responder ↓

23. Julia en 24 de septiembre de 2012 en 11:28 dijo:

…Y tantas y tantas cosas que no sabemos. Incluso los medicamentos que "supuestamente" son aconsejables, te curan de cosas y te perjudican en otras. Mi marido toma medicación entre otras cosas, para el colesterol y se está perdiendo oído; en este caso, ya nos lo había advertido su médico de cabecera. El tema de la salud es tan delicado…y desde luego las dueños de las multinacionales farmacéuticas, son los putos amos del mundo.

Responder ↓

24. Anónimo en 24 de septiembre de 2012 en 11:31 dijo:

Me parece bien divulgar los abusos y fraudes pero también hay que difundir los avances cientificos que han supuesto grandes beneficios para la salud de las personas.

Responder ↓

- kanguelo en 24 de septiembre de 2012 en 12:16 dijo:

  Recuerdo una vez cómo publicaban en los medios que determinadas algas habían tenido resultados positivos en la lucha contra el sarcoma, uno de los cánceres más agresivos. Y fuimos esperanzados al oncólogo; uno nos remitió a otro, y el otro a un tercero que conocía el experimento para terminar reconociendo que no nos fiáramos de lo que aparecía publicado, que la mayoría de las ocasiones se publican cosas no ajustadas a la realidad con el fin de conseguir inversiones…
  Creo que se deben mejorar los controles y que el estado debería asumir el campo de la investigación para evitar estos fraudes que guardan intereses económicos. Sólo la investigación pública a través del estado o universidades públicas, creo, que es lo que nos puede permitir mayores avances.
  Un saludo.

  Responder ↓

25. kanguelo en 24 de septiembre de 2012 en 12:02 dijo:

A veces, por mor del dinero, la ciencia se convierte en dogma… y eso pasa con las farmacéuticas, que tratan de cronificar las enfermedades.

Responder ↓

26. Cristian en 24 de septiembre de 2012 en 12:04 dijo:

En España, desde la última modificación de la legislación sobre investigación biomédica y ensayos clínicos, ya no se permite obviar los resultados negativos, y para que la AEMPS apruebe el fármaco, el promotor debe aportar todos los estudios realizados, incluso los que aportan datos negativos. ¿Cómo se sabe que no ha aportado algún ensayo clínico? Porque existe un registro europeo de EE.CC, cuyo número de registro es necesario para que se pueda iniciar el experimento.

Responder ↓

27. FDN en 24 de septiembre de 2012 en 12:08 dijo:

Los medicamentos antidepresivos han mejorado mucho la cálidos de vida de las personas

afectadas por la depresión. No caigamos en generalizaciones que pueden causar mucho daño.

Responder ↓

28. chabi en 24 de septiembre de 2012 en 12:48 dijo:

    Quizás también habría que valorar la poca duración de las patentes, ya que se registran en bloque principios químicos sin saber sus posibles efectos terapéuticos y luego se desarrollan, desarrollo que cuesta cientos de millones y muchas veces sin resultado positivo.
    La industria farmacéutica es un gran negocio, pero nadie parece jugar limpio, los fabricantes de genéricos que no investigan y aprovechan desarrollos como si cayeran del cielo, los estados que se lavan las manos como si ellos careciesen de responsabilidad al autorizar un medicamento, los ejecutivos de la industria rentabilizando inversiones de manera poco ética etc.
    Pero lo que es claro es que los laboratorios son necesarios y son un negocio, si ganan más en cosmética que en quimioterapia investigarán en cosmética, no son ONG's.
    No soy un experto ¡y vaya si se nota! dirán muchos, pero creo que no se analizan todos los datos y se carga en exceso la responsabilidad sobre una parte, hay que mejorar la regulación a nivel mundial, hay que permitir una explotación a más largo plazo pero exigiendo que los beneficios sean razonables, coño que los malvados laboratorios me han salvado la vida al menos dos veces, analicemos todo.

    Responder ↓

29. fisio en 24 de septiembre de 2012 en 13:40 dijo:

    El final es de risa. Esto se debe a la falta de regulación? Perdona pero no es precisamente el Estado el que gasta miles de millones de nuestros impuestos en comprar fármacos fraudulentos? No está la sanidad pública regulada? No está estatalizada? De risa vamos. Mejor si te hubieras guardado tu opinión política para tí, porque decir que la economía con un político presidiendo cada caja de ahorros, un banco de España, un BCE regulando cada transacción o la sanidad van mal por el "libre mercado"…

    Te has lucido.

    Responder ↓

    - kanguelo en 24 de septiembre de 2012 en 18:14 dijo:

      Por eso mismo, porque quienes están encargados de la regulación y supervisión de estas cosas es gente de ideología neoliberal que obedece más a sus amos del mercado que al interés público.
      Hay connivencias que van más allá…

      Responder ↓

30. Pingback: Cómo las farmacéuticas engañan a médicos y pacientes | Boletín Informativo de la Sanidad Pública

31. CASIREPUBLICANO en 24 de septiembre de 2012 en 15:20 dijo:

    phizer siempre estafando,

    un buen documental , PSIQUIATRIA INDUSTRIA DE MUERTE

    Responder ↓

32. Anónimo en 24 de septiembre de 2012 en 15:21 dijo:

    Es muy lícito que las Farmaceuticas ganen dinero, claro está pero de lo que hablamos es de FALSEAR LOS DATOS DE LOS ENSAYOS CLINICOS, DE LA PUBLICIDAD ENGAÑOSA SOBRE LOS EFECTOS DE LOS MEDICAMENTOS. leo algun comentario

muy poco lucido y Snada lúcido.

Responder ↓

33. Leo Muñoz Garcia en 24 de septiembre de 2012 en 15:53 dijo:

¿ESTO LO SABEN LAS ASOCIACIONES DE ENFERMOS, USUARIOS, COLEGIO DE MEDICOS…ETC?

Responder ↓

34. Anónimo en 24 de septiembre de 2012 en 16:36 dijo:

La mayor parte de los medicamentos retirados de la financiación pública recientemente en España es por falta de evidencias en la eficacia clínica y entonces la preunta es ¿Por qué se aprobaron?

Responder ↓

35. Miguel en 24 de septiembre de 2012 en 17:36 dijo:

Y Herbalife®??? eso si que es una secta estafadora de estructura piramidal como Afinsa y Forum.

Responder ↓

36. curloys en 24 de septiembre de 2012 en 17:53 dijo:

Lamentable el artículo… Este señor que escribe no tiene ni la más minima idea de ciencia, ni tampoco (por el escaso desarrollo del panfleto) tiene, ni zorra idea, de lo que denomina ‘regulación’

Responder ↓

37. Beatriz Basenji en 24 de septiembre de 2012 en 18:13 dijo:

En la mayoría de los casos los médicos recetan dosis mucho mas altas que las necesarias.Suele suceder con los corticoides,que medican 4 dosis, cuando con UNA SOLA diaria es suficiente.

Responder ↓

38. Anónimo en 24 de septiembre de 2012 en 18:25 dijo:

Mi querido curloys hace falta algo más que insultos, no aportas ni un solo argumento y me parece que si alguien no tiene ni npi ese eres tú.

Responder ↓

39. fabricio en 24 de septiembre de 2012 en 18:27 dijo:

Por no hablar del SIDA

Responder ↓

40. antitooo en 24 de septiembre de 2012 en 18:40 dijo:

es demencial el mercado libre de esta ramera sociedad capitalista…sino se termina con el, élterminara con la Hum,anidad

Responder ↓

41. Pingback: Ferran Sala Casasampere » Cómo las farmacéuticas engañan a médicos y pacientes

42. Lume en 24 de septiembre de 2012 en 19:18 dijo:

Es correcta la generalización? A las pequeñas empresas están muy controladas. Infórmese de los pasos que hay que seguir para sacar un medicamento al mercado.

Responder ↓

43. Luis en 24 de septiembre de 2012 en 19:29 dijo:

    La peli “EL jardinero fiel“ trata este tema.

    Responder ↓

44. FDN en 24 de septiembre de 2012 en 20:43 dijo:

    Una cosa es la EFICACIA de un medicamento en un ensayo clínico en el que los pacientes tienen que cumplir unos requisitos y otra la EFECTIVIDAD en la práctica clínica con pacientes reales que no cumplen con los requisitos de los ensayos y no tienen porque reproducir los mismos resultados.

    Responder ↓

45. CideHamete en 24 de septiembre de 2012 en 22:10 dijo:

    Éste es un tema muy complejo en el que, para empezar, el autor debería haber evitado un título tan escurridizo sólo para llamar la atención. El sistema de desarrollo en fases clínicas de una molécula hasta convertirse en producto farmacéutico comercializado y posteriormente a su puesta en el mercado es la base angular del sistema terapéutico y enormemente fiable. Además, no hay industria tan regulada como la farmacéutica hasta el punto de que al tener los precios intervenidos (como el caso de España) está contribuyendo a una desaceleración en el desarrollo de nuevos fármacos por falta de retorno de la inversión, que como como todo el mundo entende es uno de los objetivos de cualquer industria. Otra cosa es que lo que “determinadas” farmacéuticas decidan hacer para ganar dinero. Curiosamente suelen ser las más poderosas las que suelen estar involucradas en prácticas poco honestas. A estas alturas no es de recibo que no se obligue a publicar cualquier ensayo clínico que se ponga en marcha como tampoco es entendible la nula práctica de declaración de conflicto de intereses de los médicos que hablan para las farmacéuticas, ql menos en España.

    Responder ↓

46. Mikel en 24 de septiembre de 2012 en 22:52 dijo:

    Hala, se pone un titular así y nos quedamos tan anchos… Errores y malas prácticas ha habido seguro, pero muuuuucchos menos que aciertos y buen hacer. Gracias, entre otras cosas, a medicamentos como esos que usamos cuando nos ponemos malos, o cuando enfermamos de forma severa, hemos ganado en calidad de vida, cuando no, directamente, hemos salvado la vida o hemos visto a un amigo o familiar superar, por ejemplo, un proceso oncológico. Cuidado con la demagogia…

    Responder ↓

47. robert en 25 de septiembre de 2012 en 00:39 dijo:

    http://ipsn.es/video/peticion/Peticion1209.html

    Responder ↓

48. jdj en 25 de septiembre de 2012 en 10:26 dijo:

    Como todo en la vida es relativo, según los ojos del que los vé. La administración y ciertos sectores radicalizados mienten a la población con los genéricos, son iguales, “sí”, pero si se hicieran las cosas bien ,con controles de bioequivalencia. Lo que no es de recibo es que te tomes un un inhibidor de la bomba de protones, por ejempo, y te ” ardores” y te tomes otro de marca y te lo mejore.

    Responder ↓

49. Erizo en 25 de septiembre de 2012 en 14:17 dijo:

    El titular del artículo es claramente MANIPULADOR, luego su autor ENGAÑA a los

lectores y pacientes, reales o potenciales, cuando escribe LAS farmacéuticas y luego cuenta los pecados de SÓLO DOS de ellas.

¿Puede demostrar que LAS demás hacen lo mismo?

¡¡Asco de "periodismo" fraudulento!!

Responder ↓

- Alguien que cree en la ciencia en 25 de septiembre de 2012 en 19:58 dijo:

  Totalmente de acuerdo.
  Pura demagogia.

  S2

  Responder ↓

50. mayone en 25 de septiembre de 2012 en 16:19 dijo:

Es de pena lo que hacen con nosotros. Lo de las farmacéuticas es algo sabido y el que haya algunas mejores que otras, si creo que deben ser medidas todas por el mismo rasero.

Responder ↓

51. Alguien que cree en la ciencia en 25 de septiembre de 2012 en 19:14 dijo:

Estoy alucinando con vuestros comentarios, ahora todos a poner en duda todos los medicamentos. Yo de vosotros no volvería a ir al médico nunca más. Ir al curandero que seguro que os va mejor

Responder ↓

- Lewis en 25 de septiembre de 2012 en 20:46 dijo:

  Bastante mejor en no pocos casos, muchos médicos estarían mejor en sus casas que cronificando enfermedades o matando enfermos.

  Responder ↓

  - Alguien que cree en la ciencia en 25 de septiembre de 2012 en 22:42 dijo:

    Eres un demagogo !!

  - Lewis en 26 de septiembre de 2012 en 07:25 dijo:

    Tú muchísimo más demagogo aún, "poseedor de la verdad científica"

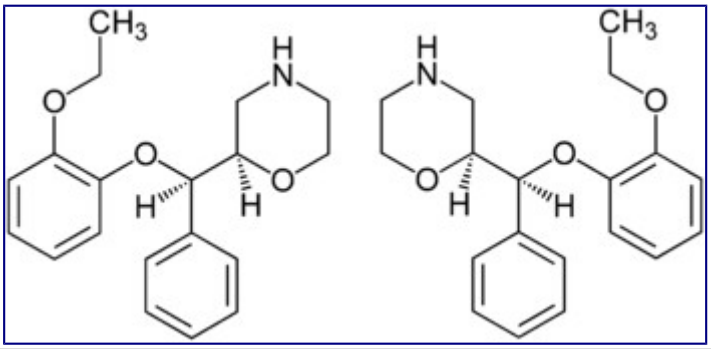
MÁS CONTENIDOS DE PRINCIPIA MARSUPIA EN NUESTRA PÁGINA DE FACEBOOK

Principia Marsupia en Facebook

Reboxetine

From Wikipedia, the free encyclopedia

Reboxetine



Systematic (IUPAC) name	
(*R**,*R**)-2-[(2-ethoxyphenoxy)-phenyl-methyl]morpholine	
Clinical data	
Pregnancy cat.	?
Legal status	℞ Prescription only
Routes	Oral
Pharmacokinetic data	
Bioavailability	94.5%[1]
Protein binding	98%
Metabolism	Hepatic, CYP3A4-mediated
Half-life	13 hours[2]
Excretion	Renal
Identifiers	
CAS number	98769-81-4 ✓
ATC code	N06AX18
PubChem	CID 127151
DrugBank	DB00234
ChemSpider	112870 ✓
UNII	947S0YZ36I ✓
KEGG	D08472 ✓
ChEMBL	CHEMBL14370 ✗
Chemical data	
Formula	$C_{19}H_{23}NO_3$
Mol. mass	313.391 g/mol

SMILES[show]

InChI[show]

✗ **(what is this?) (verify)**

Reboxetine is a drug marketed as an antidepressant for use in the treatment of clinical depression, panic disorder and ADD/ADHD, developed by Pharmacia (now Pfizer). Its mesylate (*i.e.*

methanesulfonate) salt is sold under tradenames including **Edronax**, **Norebox**, **Prolift**, **Solvex**, **Davedax** or **Vestra**. It is approved for use in many European countries, but has not been approved for use in the United States because of a lack of proven efficacy.

According to a meta-analysis of 12 new-generation antidepressants, reboxetine was no more effective than placebo, was "significantly less" effective, and was less acceptable, than the other drugs in treating the acute-phase treatment of adults with unipolar major depression.[3][4][5]

According to a systematic review and meta-analysis by IQWiG, including unpublished data, published data on reboxetine overestimated the benefit of reboxetine versus placebo by up to 115% and reboxetine versus SSRIs by up to 23%, and also underestimated harm, concluding that reboxetine was an ineffective and potentially harmful antidepressant. The study also showed that nearly three quarters of the data on patients who took part in trials of reboxetine were not published by Pfizer until now.[6][7]

Reboxetine has two chiral centers. Thus, four stereoisomers may exist, the (*R*,*R*)-, (*S*,*S*)-, (*R*,*S*)-, and (*S*,*R*)-isomers. The active ingredient of reboxetine is a racemic mixture of two enantiomers, the (*R*,*R*)-(–)- and (*S*,*S*)-(+)-isomer.[8]

Mode of action

Unlike most antidepressants on the market, reboxetine is a norepinephrine reuptake inhibitor (NRI); it does not inhibit the reuptake of serotonin.[9]

Side effects

Common side effects of reboxetine include: dry mouth, constipation, headache, drowsiness, dizziness, excessive sweating and insomnia. Hypertension has been infrequently seen.

In 4 to 8% of all patients treated the medication has to be discontinued due to following reasons (percentages represent mean values):

- insomnia 1.3%
- excessive sweating 1.1%
- vertigo/hypotension and paraesthesia 0.8%
- dizziness, impotence, and other urological problems 0.5% each

Some other rare side effects include anxiety, loss of appetite, loss of libido, urinary retention in men, pain on ejaculation, increased orgasm intensity, and premature/quickened ejaculation.

Reboxetine is normally well tolerated. So far no attributable fatalities have been noted.

Metabolism

Both the (*R*,*R*)-(–) and (*S*,*S*)-(+)-enantiomers of reboxetine are predominantly metabolized by the CYP3A4 isoenzyme.[10] The primary metabolite of reboxetine is *O*-desethylreboxetine, and there are also three minor metabolites—Phenol A, Phenol B, and UK1, Phenol B being the most minor.[10]

Interactions with other medications

Because of its reliance on CYP3A4, reboxetine *O*-desethylation is markedly inhibited by papaverine and ketoconazole.[10]

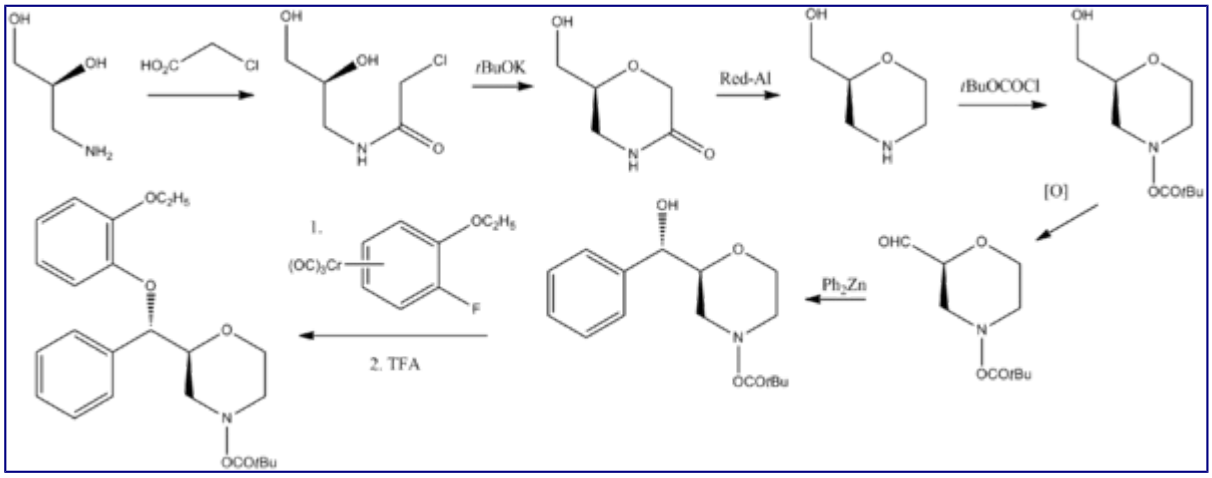
According to Weiss *et al.*, reboxetine is an intermediate-level inhibitor of P-glycoprotein, which gives it the potential to interact with ciclosporin, tacrolimus, paroxetine, sertraline, quinidine, fluoxetine, fluvoxamine.[11]

The potency and duration of the effects of benzodiazepines can be increased because reboxetine interferes with their excretion.

History

By mid-2007, reboxetine was licensed worldwide in over 50 countries, including Italy, Germany and the United Kingdom. In May 2007, however, the Food and Drug Administration declined Pharmacia's license application for the American market. Therefore it is yet to be available in the United States.

Chemistry



[12]

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2. ^ Edwards DM, Pellizzoni C, Breuel HP, Berardi A, Castelli MG, Frigerio E, Poggesi I, Rocchetti M, Dubini A, Strolin Benedetti M (1995). "Pharmacokinetics of reboxetine in healthy volunteers. Single oral doses, linearity and plasma protein binding". *Biopharmaceutics & Drug Disposition* **16** (6): 443–60. doi:10.1002/bdd.2510160603. PMID 7579027.
3. ^ Analysis shows sertraline and escitalopram are the best of 12 new-generation antidepressants Lancet Public release date: 28-Jan-2009
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5. ^ Zoloft, Lexapro the Best of Newer Antidepressants, HealthDay News, Washington Post, January 29, 2009
6. ^ Reboxetine for acute treatment of major depression: systematic review and meta-analysis

of published and unpublished placebo and selective serotonin reuptake inhibitor controlled trials British Medical Journal Public release date: 12-Oct-2010
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10. ^ *a b c* Wienkers LC, Allievi C, Hauer MJ, Wynalda MA. (1999). "Cytochrome P-450-Mediated Metabolism of the Individual Enantiomers of the Antidepressant Agent Reboxetine in Human Liver Microsomes". *Drug Metabolism & Disposition* **27** (11): 1334–1340. PMID 10534319.
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External links

- Reboxetine: A Novel Antidepressant

v t e
Stimulants (N06B)

Adamantanes	• Adaphenoxate Adapromine Amantadine Bromantane Chlodantane • Gludantane Memantine Midantane
Adenosine antagonists	• 8-Chlorotheophylline 8-Cyclopentyltheophylline 8-Phenyltheophylline Aminophylline Caffeine CGS-15943 • Dimethazan Paraxanthine SCH-58261 Theobromine Theophylline
Alkylamines	• Cyclopentamine Cypenamine Cyprodenate Heptaminol Isometheptene Methylhexaneamine Octodrine Propylhexedrine • Tuaminoheptane
Arylcyclohexylamines	• Benocyclidine Dieticyclidine Esketamine Eticyclidine Gacyclidine • Ketamine Phencyclamine Phencyclidine Rolicyclidine Tenocyclidine Tiletamine
Benzazepines	• 6-Br-APB SKF-77434 SKF-81297 SKF-82958
Cholinergics	• A-84,543 A-366,833 ABT-202 ABT-418 AR-R17779 Altinicline • Anabasine Arecoline Cotinine Cytisine Dianicline Epibatidine • Epiboxidine GTS-21 Ispronicline Nicotine PHA-543,613 • PNU-120,596 PNU-282,987 Pozanicline Rivanicline Sazetidine A

	• SIB-1553A SSR-180,711 TC-1698 TC-1827 TC-2216 TC-5619 • Tebanicline UB-165 Varenicline WAY-317,538
Convulsants	• Anatoxin-a Bicuculline DMCM Flurothyl Gabazine Pentetrazol • Picrotoxin Strychnine Thujone
Eugeroics	• Adrafinil Armodafinil CRL-40941 Modafinil
Oxazolines	• 4-Methylaminorex Aminorex Clominorex Cyclazodone Fenozolone • Fluminorex Pemoline Thozalinone
Phenethylamines	• 1-(4-Methylphenyl)-2-aminobutane 1-Phenyl-2-(piperidin-1-yl)pentan-3-one 1-Methylamino-1-(3,4-methylenedioxyphenyl)propane 2-Fluoroamphetamine 2-Fluoromethamphetamine 2-OH-PEA 2-Phenyl-3-aminobutane • 2-Phenyl-3-methylaminobutane 2,3-MDA 3-Fluoroamphetamine • 3-Fluoroethamphetamine 3-Fluoromethcathinone 3-Methoxyamphetamine 3-Methylamphetamine 3,4-DMMC • 4-BMC 4-Ethylamphetamine 4-FA 4-FMA 4-MA 4-MMA 4-MTA • 6-FNE AL-1095 Alfetamine a-Ethylphenethylamine Amfecloral • Amfepentorex Amfepramone Amidephrine 2-Amino-1,2-dihydronaphthalene 2-Aminoindane 5-(2-Aminopropyl)indole • 2-Aminotetralin Amphetamine (Dextroamphetamine, Levoamphetamine) Amphetaminil Arbutamine ß-Methylphenethylamine ß-Phenylmethamphetamine Benfluorex • Benzedrone Benzphetamine BDB BOH 3-Benzhydrylmorpholine • BPAP Buphedrone Bupropion Butylone Camfetamine Cathine • Cathinone Chlorphentermine Cilobamine Cinnamedrine Clenbuterol Clobenzorex Cloforex Clortermine Cypenamine • D-Deprenyl Denopamine Dimethoxyamphetamine Dimethylamphetamine Dimethylcathinone Dobutamine DOPA (Dextrodopa, Levodopa) Dopamine Dopexamine Droxidopa EBDB • Ephedrine Epinephrine Epinine Etafedrine Ethcathinone Ethylamphetamine Ethylnorepinephrine Ethylone Etilefrine Famprofazone Fenbutrazate Fencamfamine Fencamine Fenethylline • Fenfluramine (Dexfenfluramine, Levofenfluramine) Fenmetramide • Fenproporex Feprosidnine Flephedrone Fludorex Furfenorex G-130 • Gepefrine Hexapradol HMMA Hordenine Hydroxyamphetamine • 5-Iodo-2-aminoindane Ibopamine IMP Indanylamphetamine • Iofetamine Isoetarine Isoethcathinone Isoprenaline L-Deprenyl (Selegiline) Lefetamine Lisdexamfetamine Lophophine Manifaxine • MBDB MDA MDBU MDEA MDMA MDMPEA MDOH MDPR • MDPEA Mefenorex Mephedrone Mephentermine Metanephrine • Metaraminol Mesocarb Methamphetamine Dextromethamphetamine, Levomethamphetamine) Methoxamine • Methoxyphenamine MMA Methcathinone Methedrone Methoxyphenamine Methylone MMDA MMDMA MMMA Morazone N-Benzyl-1-phenethylamine N,N-Dimethylphenethylamine Naphthylamphetamine Nisoxetine

	Norepinephrine Norfenefrine Norfenfluramine Normetanephrine • L-Norpseudoephedrine Octopamine Orciprenaline Ortetamine Oxilofrine PBA PCA PHA Pargyline Pentorex Pentylone Phenatine • Phendimetrazine Phenmetrazine Phenpromethamine Phentermine • Phenylalanine 2-Phenyl-3,6-dimethylmorpholine Phenylephrine • Phenylpropanolamine Pholedrine PIA PMA PMEA PMMA PPAP • Phthalimidopropiophenone Prenylamine Propylamphetamine • Pseudoephedrine Pseudophenmetrazine Radafaxine Ropinirole • Salbutamol (Levosalbutamol) Sibutramine Synephrine Theodrenaline Tiflorex Tranylcypromine Tyramine Tyrosine • Xylopropamine Zylofuramine
Piperazines	• 2C-B-BZP BZP CM156 DBL-583 GBR-12783 GBR-12935 GBR-13069 GBR-13098 GBR-13119 MeOPP MBZP Vanoxerine
Piperidines	• 1-Benzyl-4-(2-(diphenylmethoxy)ethyl)piperidine 1-(3,4-Dichlorophenyl)-1-(piperidin-2-yl)butane 2-Benzylpiperidine • 2-Methyl-3-phenylpiperidine 3,4-Dichloromethylphenidate • 4-Benzylpiperidine 4-Methylmethylphenidate Desoxypipradrol • Difemetorex Diphenylpyraline Ethylphenidate Methylnaphthidate • Methylphenidate (Dexmethylphenidate) N-Methyl-3ß-propyl-4ß-(4-chlorophenyl)piperidine Nocaine Phacetoperane Pipradrol SCH-5472
Pyrrolidines	• 2-Diphenylmethylpyrrolidine a-PPP a-PBP a-PVP Diphenylprolinol • MDPPP MDPBP MDPV MPBP MPHP MPPP MOPPP Naphyrone • PEP Prolintane Pyrovalerone
Tropanes	• 3-CPMT 3'-Chloro-3a-(diphenylmethoxy)tropane 3-Pseudotropyl-4-fluorobenzoate 4'-Fluorococaine AHN-1055 Altropane (IACFT) • Brasofensine CFT (WIN 35,428) ß-CIT (RTI-55) Cocaethylene • Cocaine Dichloropane (RTI-111) Difluoropine FE-ß-CPPIT • FP-ß-CPPIT Ioflupane (^{123}I) Norcocaine PIT PTT RTI-31 RTI-32 • RTI-51 RTI-105 RTI-112 RTI-113 RTI-117 RTI-120 RTI-121 (IPCIT) RTI-126 RTI-150 RTI-154 RTI-171 RTI-177 RTI-183 • RTI-193 RTI-194 RTI-199 RTI-202 RTI-204 RTI-229 RTI-241 • RTI-336 RTI-354 RTI-371 RTI-386 Salicylmethylecgonine • Tesofensine Troparil (ß-CPT, WIN 35,065-2) Tropoxane WF-23 • WF-33 WF-60
Others	• 1-(Thiophen-2-yl)-2-aminopropane 2-MDP 2-Phenylcyclohexylamine 3,3-Diphenylcyclobutanamine Amfonelic acid Amineptine Amiphenazole Atipamezole Atomoxetine Bemegride Benzydamine BTQ BTS 74,398 Carphedon Ciclazindol • Clofenciclan Cropropamide Crotetamide D-161 Diclofensine Dimethocaine Efaroxan Etamivan EXP-561 Fenpentadiol Gamfexine Gilutensin GSK1360707F GYKI-52895 Hexacyclonate • Idazoxan Indanorex Indatraline JNJ-7925476 JZ-IV-10 Lazabemide • Leptacline Levopropylhexedrine Lomevactone LR-5182 Mazindol • Meclofenoxate Medifoxamine Mefexamide Methastyridone

- Methiopropamine N-Methyl-3-phenylnorbornan-2-amine Nefopam
- Nikethamide Nomifensine O-2172 Oxaprotiline PNU-99,194
- Propylhexedrine PRC200-SS Rasagiline Rauwolscine Rubidium chloride Setazindol Tametraline Tandamine Trazium UH-232
- Yohimbine

See also Sympathomimetic amines

v t e

Antidepressants (N06A)

Specific reuptake inhibitors (RIs), enhancers (REs), and releasing agents (RAs)

Selective serotonin reuptake inhibitors (SSRIs)	• Alaproclate Citalopram • Escitalopram Femoxetine • Fluoxetine[#] Fluvoxamine • Indalpine Ifoxetine Litoxetine Lubazodone • Omiloxetine Panuramine • Paroxetine Pirandamine • Seproxetine Sertraline[#] • Zimelidine[‡]
Serotonin–norepinephrine reuptake inhibitors (SNRIs)	• Clovoxamine Desvenlafaxine Duloxetine • Levomilnacipran Eclanamine Milnacipran • Sibutramine Venlafaxine
Serotonin–norepinephrine–dopamine reuptake inhibitors (SNDRIs)	• Amitifadine Bicifadine • Brasofensine BTS-74,398 • Cocaine Diclofensine • DOV-21,947 DOV-102,677 • DOV-216,303 EXP-561 • Fezolamine JNJ-7925476 • NS-2359 PRC200-SS • Pridefine SEP-225,289 • SEP-227,162 Tesofensine
Norepinephrine reuptake inhibitors (NRIs)	• Amedalin • Atomoxetine/Tomoxetine • Binedaline Ciclazindol • Daledalin Edivoxetine • Esreboxetine Lortalamine • Mazindol Nisoxetine • **Reboxetine** • Talopram Talsupram

Dopamine reuptake inhibitors (DRIs)	• Tandamine Viloxazine • Medifoxamine Vanoxerine
Norepinephrine-dopamine reuptake inhibitors (NDRIs)	• Amineptine • Bupropion/Amfebutamone[#] • Cilobamine Manifaxine • Methylphenidate Nomifensine Radafaxine • Tametraline
Norepinephrine-dopamine releasing agents (NDRAs)	• Amphetamine Befuraline • Lisdexamfetamine • Methamphetamine • Phenethylamine Piberaline • Tranylcypromine
Serotonin-norepinephrine-dopamine releasing agents (SNDRAs)	• 4-Methyl-αMT αET/Etryptamine • αMT/Metryptamine
Selective serotonin reuptake enhancers (SSREs)	• Tianeptine
Others	• Indeloxazine Teniloxazine • Tramadol Viqualine

Receptor antagonists and/or reuptake inhibitors

Serotonin antagonists and reuptake inhibitors (SARIs)	• Etoperidone Nefazodone Trazodone
Noradrenergic and specific serotonergic antidepressants (NaSSAs)	• Aptazapine • Esmirtazapine • Mianserin Mirtazapine • Setiptiline/Teciptiline
Norepinephrine-dopamine disinhibitors (NDDIs)	• Agomelatine
Serotonin modulators and stimulators (SMSs)	• Vortioxetine
Others	• Tedatioxetine • Vilazodone

Bicyclics	• Tiazesim Tofenacin
Tricyclics	• Amezepine Amineptine • Amitriptyline[#] • Amitriptylinoxide • Azepindole Butriptyline • Cianopramine Clomipramine Cotriptyline Cyanodothiepin • Demexiptiline • Depramine/Balipramine • Desipramine Dibenzepin • Dimetacrine • Dosulepin/Dothiepin • Doxepin Enprazepine • Fluotracen Hepzidine • Homopipramol Imipramine • Imipraminoxide • Intriptyline Iprindole • Ketipramine Litracen • Lofepramine Losindole • Mariptiline Melitracen • Metapramine Mezepine • Naranol Nitroxazepine • Nortriptyline Noxiptiline • Octriptyline Opipramol • Pipofezine Propizepine • Protriptyline Quinupramine Tampramine Tianeptine • Tienopramine Trimipramine
Tetracyclics	• Amoxapine Aptazapine • Azipramine Ciclazindol • Ciclopramine Esmirtazapine Maprotiline Mazindol • Mianserin Mirtazapine • Oxaprotiline • Setiptiline/Teciptiline

Monoamine oxidase inhibitors (MAOIs)

Nonselective	• *Irreversible:* Benmoxin

	• Carbenzide Cimemoxin • Domoxin Echinopsidine • Iproclozide Iproniazid • Isocarboxazid Mebanazine • Metfendrazine Nialamide • Octamoxin Phenelzine • Pheniprazine • Phenoxypropazine • Pivalylbenzhydrazine • Safrazine • Tranylcypromine
	• *Reversible:* Caroxazone • Paraxazone Quercetin
	• *Irreversible:* Clorgiline
MAO_A-Selective	• *Reversible:* Amiflamine • Bazinaprine Befloxatone • Befol Berberine Brofaromine • Cimoxatone Esuprone • Harmala Alkaloids (Harmine • Harmaline Tetrahydroharmine • Harman Norharman, etc) • Methylene Blue Metralindole • Minaprine Moclobemide • Pirlindole Sercloremine • Tetrindole Toloxatone • Tyrima
MAO_B-Selective	• *Irreversible:* Ladostigil • Mofegiline Pargyline • Rasagiline Selegiline • *Reversible:* Lazabemide • Milacemide

Azapirones and other $5\text{-}HT_{1A}$ receptor agonists

- Alnespirone Aripiprazole Befiradol Buspirone Eptapirone Flesinoxan Flibanserin Gepirone Ipsapirone Oxaflozane Tandospirone Vilazodone
- Zalospirone

- #WHO-EM ‡Withdrawn from market Clinical trials: †Phase III §Never to phase III

M: PSO/PSI mepr dsrd (o, p, m, p, a, d, s), sysi/epon, proc(eval/thrp),

v t e

Psychostimulants, agents used for ADHD, and nootropics (N06B)

Centrally acting sympathomimetics		• Amphetamine Amphetaminil • Atomoxetine • Dexmethylphenidate • Dextroamphetamine • Dextromethamphetamine • Fencamfamine Fenethylline • Lisdexamfetamine • Methylphenidate Mesocarb • Pemoline Pipradrol Prolintane
Xanthine derivatives		• Caffeine Fenethylline
Glutamate receptor	**Racetams**	• Aniracetam • Nefiracetam • Noopept • Oxiracetam • Phenylpiracetam • Piracetam • Pramiracetam
	Ampakines	• CX-516 CX-546 • CX-614 CX-691 • CX-717 IDRA-21 • LY-404,187 • LY-503,430 • PEPA S-18986 • Sunifiram Unifiram
Eugeroics / Benzhydryl compounds		• Adrafinil Armodafinil Modafinil
Histamine H3 receptor antagonists		• A-349,821 ABT-239 Ciproxifan • GSK-189,254
$GABA_A$ α_5 inverse agonists		• α_5IA L-655,708 PWZ-029 • Suritozole TB-21007 ZK-93426
Dopamine D1 receptor agonists		• A-77636 Dihydrexidine Dinapsoline Doxanthrine SKF-81297 6-Br-APB Clozapine
α7 nicotinic agonists / PAMs		• AR-R17779 PNU-282,987 • SSR-180,711
Prolyl endopeptidase inhibitors		• S-17092

Alpha-adrenergic agonists	• Clonidine Guanfacine
Plants	• Paullinia cupana (Guarana) • Eleutherococcus senticosus
Antioxidants	• Stabilized R-(+)-lipoic acid (RLA)
Other psychostimulants and nootropics	• Acetylcarnitine Adafenoxate • Bifemelane Carbenoxolone • Citicoline Cyprodenate Ensaculin Idebenone • Ispronicline Deanol Dimebon • Fipexide Leteprinim Linopirdine • Meclofenoxate Nizofenone P7C3 Pirisudanol Pyritinol • Rubidium Sulbutiamine Taltirelin Tricyanoaminopropene • Vinpocetine Phosphatidylserine • Tyrosine

M: PSO/PSI	mepr	dsrd (o, p, m, p, a, d, s), sysi/epon, spvo	proc(eval/thrp), drug(N5A/5B/5C/6A/6B/6D)

v t e
Adrenergics

Receptor ligands

α_1

- **Agonists**: 5-FNE 6-FNE Amidephrine Anisodamine Anisodine Cirazoline Dipivefrine
- Dopamine Ephedrine Epinephrine Etilefrine Ethylnorepinephrine Indanidine Levonordefrin Metaraminol Methoxamine Methyldopa Midodrine Naphazoline Norepinephrine Octopamine Oxymetazoline Phenylephrine Phenylpropanolamine
- Pseudoephedrine Synephrine Tetrahydrozoline
  Antagonists: Abanoquil Adimolol Ajmalicine Alfuzosin Amosulalol Arotinolol Atiprosin
- Benoxathian Buflomedil Bunazosin Carvedilol CI-926 Corynanthine Dapiprazole
- DL-017 Domesticine Doxazosin Eugenodilol Fenspiride GYKI-12,743 GYKI-16,084
- Indoramin Ketanserin L-765,314 Labetalol Mephendioxan Metazosin Monatepil Moxisylyte Naftopidil Nantenine Neldazosin Nicergoline Niguldipine Pelanserin
- Phendioxan Phenoxybenzamine Phentolamine Piperoxan Prazosin Quinazosin Ritanserin
- RS-97,078 SGB-1,534 Silodosin SL-89.0591 Spiperone Talipexole Tamsulosin Terazosin
- Tibalosin Tiodazosin Tipentosin Tolazoline Trimazosin Upidosin Urapidil Zolertine

* Note that many TCAs, TeCAs, antipsychotics, ergolines, and some piperazines like buspirone and trazodone all

antagonize α_1-adrenergic receptors as well, which contributes to their side effects such as orthostatic hypotension.

α_2

- **Agonists**: (R)-3-Nitrobiphenyline 4-NEMD 6-FNE Amitraz Apraclonidine Brimonidine
- Cannabivarin Clonidine Detomidine Dexmedetomidine Dihydroergotamine Dipivefrine
- Dopamine Ephedrine Ergotamine Epinephrine Esproquin Etilefrine Ethylnorepinephrine
- Guanabenz Guanfacine Guanoxabenz Levonordefrin Lofexidine Medetomidine Methyldopa Mivazerol Naphazoline Norepinephrine Oxymetazoline Phenylpropanolamine Piperoxan Pseudoephedrine Rilmenidine Romifidine Talipexole
- Tetrahydrozoline Tizanidine Tolonidine Urapidil Xylazine Xylometazoline
  Antagonists: 1-PP Adimolol Aptazapine Atipamezole BRL-44408 Buflomedil Cirazoline
- Efaroxan Esmirtazapine Fenmetozole Fluparoxan GYKI-12,743 GYKI-16,084 Idazoxan
- Mianserin Mirtazapine MK-912 NAN-190 Olanzapine Phentolamine Phenoxybenzamine
- Piperoxan Piribedil Rauwolscine Rotigotine SB-269,970 Setiptiline Spiroxatrine Sunepitron Tolazoline Yohimbine

* Note that many atypical antipsychotics and azapirones like buspirone (via metabolite 1-PP) antagonize α_2-adrenergic receptors as well.

β

- **Agonists**: 2-FNE 5-FNE Amibegron Arbutamine Arformoterol Arotinolol BAAM Bambuterol Befunolol Bitolterol Broxaterol Buphenine Carbuterol Cimaterol Clenbuterol Denopamine Deterenol Dipivefrine Dobutamine Dopamine Dopexamine
- Ephedrine Epinephrine Etafedrine Etilefrine Ethylnorepinephrine Fenoterol Formoterol
- Hexoprenaline Higenamine Indacaterol Isoetarine Isoprenaline Isoxsuprine Levonordefrin Levosalbutamol Mabuterol Methoxyphenamine Methyldopa
- *N*-Isopropyloctopamine Norepinephrine Orciprenaline Oxyfedrine Phenylpropanolamine
- Pirbuterol Prenalterol Ractopamine Procaterol Pseudoephedrine Reproterol Rimiterol
- Ritodrine Salbutamol Salmeterol Solabegron Terbutaline Tretoquinol Tulobuterol
- Xamoterol Zilpaterol Zinterol
  Antagonists: Acebutolol Adaprolol Adimolol Afurolol Alprenolol Alprenoxime Amosulalol Ancarolol Arnolol Arotinolol Atenolol Befunolol Betaxolol Bevantolol
- Bisoprolol Bopindolol Bormetolol Bornaprolol Brefonalol Bucindolol Bucumolol Bufetolol Buftiralol Bufuralol Bunitrolol Bunolol Bupranolol Burocrolol Butaxamine
- Butidrine Butofilolol Capsinolol Carazolol Carpindolol Carteolol Carvedilol Celiprolol
- Cetamolol Cicloprolol Cinamolol Cloranolol Cyanopindolol Dalbraminol Dexpropranolol Diacetolol Dichloroisoprenaline Dihydroalprenolol Dilevalol Diprafenone Draquinolol Dropranolol Ecastolol Epanolol Ericolol Ersentilide Esatenolol
- Esmolol Esprolol Eugenodilol Exaprolol Falintolol Flestolol Flusoxolol Hydroxycarteolol Hydroxytertatolol ICI-118,551 Idropranolol Indenolol Indopanolol
- Iodocyanopindolol Iprocrolol Isoxaprolol Isamoltane Labetalol Landiolol Levobetaxolol
- Levobunolol Levocicloprolol Levomoprolol Medroxalol Mepindolol Metalol Metipranolol Metoprolol Moprolol Nadolol Nadoxolol Nafetolol Nebivolol Neraminol
- Nifenalol Nipradilol Oberadilol Oxprenolol Pacrinolol Pafenolol Pamatolol Pargolol
- Parodilol Penbutolol Penirolol PhQA-33 Pindolol Pirepolol Practolol Primidolol Procinolol Pronethalol Propafenone Propranolol Ridazolol Ronactolol Soquinolol Sotalol
- Spirendolol SR 59230A Sulfinalol TA-2005 Talinolol Tazolol Teoprolol Tertatolol Terthianolol Tienoxolol Tilisolol Timolol Tiprenolol Tolamolol Toliprolol Tribendilol
- Trigevolol Xibenolol Xipranolol

Reuptake inhibitors

- *Selective norepinephrine reuptake inhibitors*: Amedalin Atomoxetine (Tomoxetine)

VMAT

- Ibogaine Reserpine Tetrabenazine

Releasing agents

- *Morpholines*: Fenbutrazate Fenmetramide Morazone Phendimetrazine Phenmetrazine Pseudophenmetrazine; *Oxazolines*: 4-MAR Aminorex Clominorex
- Cyclazodone Fenozolone Fluminorex Pemoline Thozalinone; *Phenethylamines* (also *amphetamines*, *cathinones*, etc): 2-OH-PEA 4-CAB 4-FA 4-FMA 4-MA
- 4-MMA Alfetamine Amfecloral Amfepentorex Amfepramone Amphetamine (Dextroamphetamine Levoamphetamine) Amphetaminil β-Me-PEA BDB Benzphetamine BOH Buphedrone Butylone Cathine Cathinone Clobenzorex Clortermine Dimethylamphetamine Dimethylcathinone DMA DMMA EBDB Ephedrine Ethcathinone Ethylamphetamine Ethylone Famprofazone Fenethylline
- Fenproporex Flephedrone Fludorex Furfenorex Hordenine Hydroxyamphetamine
- IAP IMP Iofetamine Lisdexamfetamine Lophophine MBDB MDA MDEA MDMA MDMPEA MDOH MDPEA Mefenorex Mephedrone Mephentermine
- Methamphetamine (Dextromethamphetamine Levomethamphetamine) Methcathinone Methedrone Methylone Naphthylisopropylamine Ortetamine *p*BA
- *p*CA Pentorex Phenethylamine Pholedrine Phenpromethamine Phentermine Phenylpropanolamine *p*IA Prenylamine Propylamphetamine Pseudoephedrine
- Selegiline (also D-Deprenyl) Tiflorex Tyramine Xylopropamine Zylofuramine; *Piperazines*: 2C-B-BZP BZP MBZP mCPP MDBZP MeOPP pFPP; *Others*: 2-ADN 2-AI 2-AT 2-BP 4-BP 5-IAI Clofenciclan Cyclopentamine Cypenamine
- Cyprodenate Feprosidnine Gilutensin Heptaminol Hexacyclonate Indanorex
- Isometheptene Methylhexanamine Octodrine Phthalimidopropiophenone Propylhexedrine (Levopropylhexedrine) Tuaminoheptane

Enzyme inhibitors

Anabolism

PAH

- 3,4-Dihydroxystyrene

TH

- 3-Iodotyrosine
- Aquayamycin
- Bulbocapnine
- Metirosine Oudenone

AAAD

- Benserazide Carbidopa
- DFMD Genistein
- Methyldopa

DBH

- Bupicomide
  Disulfiram Dopastin
- Fusaric acid Nepicastat
- Phenopicolinic acid
- Tropolone

	PNMT	• CGS-19281A SKF-64139 SKF-7698
Catabolism	**MAO**	• *Nonselective*: Benmoxin Caroxazone Echinopsidine Furazolidone • Hydralazine Indantadol Iproclozide Iproniazid Isocarboxazid Isoniazid • Linezolid Mebanazine Metfendrazine Nialamide Octamoxin Paraxazone Phenelzine Pheniprazine Phenoxypropazine Pivalylbenzhydrazine Procarbazine Safrazine Tranylcypromine; *MAO-A selective*: Amiflamine Bazinaprine Befloxatone Befol Brofaromine • Cimoxatone Clorgiline Esuprone Harmala alkaloids (Harmine, Harmaline Tetrahydroharmine Harman Norharman, etc) Methylene blue Metralindole Minaprine Moclobemide Pirlindole Sercloremine • Tetrindole Toloxatone Tyrima; *MAO-B selective*: Ladostigil Lazabemide Milacemide Mofegiline Pargyline Rasagiline Safinamide • Selegiline (also [[D-Deprenyl]]) * Note that MAO-B inhibitors also influence norepinephrine/epinephrine levels since they inhibit the breakdown of their precursor dopamine.
	COMT	• Entacapone Nitecapone Tolcapone

Others	
Precursors	• L-Phenylalanine → L-Tyrosine → L-DOPA (Levodopa) → Dopamine • L-DOPS (Droxidopa)
Cofactors	• Ferrous Iron (Fe^{2+}) S-Adenosyl-L-Methionine Vitamin B_3 (Niacin • Nicotinamide → NADPH) Vitamin B_6 (Pyridoxine Pyridoxamine • Pyridoxal → Pyridoxal Phosphate) Vitamin B_9 (Folic acid → Tetrahydrofolic acid) Vitamin C (Ascorbic acid) Zinc (Zn^{2+})
Others	• *Activity enhancers*: BPAP PPAP; *Release blockers*: Bethanidine Bretylium Guanadrel Guanazodine Guanclofine Guanethidine • Guanoxan; *Toxins*: 6-OHDA

List of adrenergic drugs

Categories: Norepinephrine reuptake inhibitors Morpholines Phenol ethers

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Research

Reboxetine for acute treatment of major depression: systematic review and meta-analysis of published and unpublished placebo and selective serotonin reuptake inhibitor controlled trials

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Dirk Eyding, project manager[1], Monika Lelgemann, senior researcher[2], Ulrich Grouven, statistician[3,4], Martin Härter, head of department of medical psychology[5], Mandy Kromp, statistician[3], Thomas Kaiser, head of department of drug assessment[3], Michaela F Kerekes, data manager[3], Martin Gerken, researcher[6], Beate Wieseler, deputy head of department of drug assessment[3]
Author Affiliations

Correspondence to: B Wieseler, Institute for Quality and Efficiency in Health Care, Dillenburger Strasse 27, 51105 Cologne, Germany beate.wieseler@iqwig.de

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Abstract

Objectives To assess the benefits and harms of reboxetine versus placebo or selective serotonin reuptake inhibitors (SSRIs) in the acute treatment of depression, and to measure the impact of potential publication bias in trials of reboxetine.

Design Systematic review and meta-analysis including unpublished data.

Data sources Bibliographic databases (Medline, Embase, PsycINFO, BIOSIS, and Cochrane Library), clinical trial registries, trial results databases, and regulatory authority websites up until February 2009, as well as unpublished data from the manufacturer of reboxetine (Pfizer, Berlin).

Eligibility criteria Double blind, randomised, controlled trials of acute treatment (six weeks or more) with reboxetine versus placebo or SSRIs in adults with major depression.

Outcome measures Remission and response rates (benefit outcomes), as well as rates of patients with at least one adverse event and withdrawals owing to adverse events (harm outcomes).

Data extraction and data synthesis The procedures for data extraction and assessment of risk of bias were always conducted by one person and checked by another. If feasible, data were pooled by meta-analyses (random effects model). Publication bias was measured by comparing results of published and unpublished trials.

Results We analysed 13 acute treatment trials that were placebo controlled, SSRI controlled, or both, which included 4098 patients. Data on 74% (3033/4098) of these patients were unpublished. In the reboxetine versus placebo comparison, no significant differences in remission rates were shown (odds ratio 1.17, 95% confidence interval 0.91 to 1.51; P=0.216). Substantial heterogeneity (I^2=67.3%) was shown in the meta-analysis of the eight trials that investigated response rates for reboxetine versus placebo. A sensitivity analysis that excluded a small inpatient trial showed no significant difference in response rates between patients receiving reboxetine and those receiving placebo (OR 1.24, 95% CI 0.98 to 1.56; P=0.071; I^2=42.1%). Reboxetine was inferior to SSRIs (fluoxetine, paroxetine, and citalopram) for remission rates (OR 0.80, 95% CI 0.67 to 0.96; P=0.015) and response rates (OR 0.80, 95% CI 0.67 to 0.95; P=0.01). Reboxetine was inferior to placebo for both harm outcomes (P<0.001 for both), and to fluoxetine for withdrawals owing to adverse events (OR 1.79, 95% CI 1.06 to 3.05; P=0.031). Published data overestimated the benefit of reboxetine versus placebo by up to 115% and reboxetine versus SSRIs by up to 23%, and also underestimated harm.

Conclusions Reboxetine is, overall, an ineffective and potentially harmful antidepressant. Published evidence is affected by publication bias, underlining the urgent need for mandatory publication of trial data.

Introduction

Reboxetine, the first selective norepinephrine (noradrenaline) reuptake inhibitor used in the treatment of depression,[1] mainly acts by binding to the norepinephrine transporter and blocking reuptake of extracellular norepinephrine.[2] The drug is "indicated for the acute treatment of depressive illness or major depression and for maintaining the clinical improvement in patients initially responding to treatment."[3] Reboxetine has been approved for marketing in many European countries (for example, the United Kingdom and Germany) since 1997. In the United States, however, the application for approval was ultimately rejected after preliminary acceptance.[2] [4]

Compared with the overall amount of antidepressants prescribed, reboxetine's share is relatively small. For example, of 974 million defined daily doses of antidepressants prescribed in Germany in 2008, reboxetine accounted for 6.7 million defined daily doses.[5] The average cost of reboxetine per defined daily dose was €1.87 (£1.54; $2.39) for Edronax (Pfizer, Berlin) to €2.09 for Solvex (Merz, Frankfurt), compared with €0.52 for selective serotonin reuptake inhibitors (SSRIs), the most commonly prescribed antidepressants.[5]

Although reboxetine has been claimed to show superior efficacy to placebo and similar efficacy to other antidepressants,[1] [6] [7] [8] [9] [10] the clinical relevance of the drug has been queried. A recent systematic review by Cipriani et al[11] included a network meta-analysis of active controlled trials and found that reboxetine was not only significantly less effective than the other newer antidepressants investigated, but was also the drug with the highest dropout rates.

The German Institute for Quality and Efficiency in Health Care (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG)) conducted a health technology assessment of the short term and long term benefits and harms of reboxetine, bupropion, and mirtazapine in placebo controlled and active controlled trials of adult patients with major depressive disorder. Both published and previously unpublished data were considered. The full German language report and an English summary are available on the institute's website.[12] [13] The responsibilities and

methodological approach of IQWiG are described in its methods paper online.[14]

This publication presents the main findings of the reboxetine trials with the aim of assessing the benefits (remission and response rates) and harms (rates of patients with at least one adverse event and rates of withdrawals owing to adverse events) of reboxetine versus placebo or SSRIs in the acute treatment of major depressive disorder. In addition, for the present paper we assessed potential publication bias by comparing results from published and unpublished trials of reboxetine.

Methods

We developed and followed a standardised protocol for all steps of the review.[15]

Eligibility criteria

The health technology assessment report that formed the basis of this publication included both published and unpublished trials of reboxetine that had the following characteristics:

- Double blind, randomised controlled design
- Investigation of adult patients with major depressive disorder as their primary diagnosis according to the International Classification of Diseases, the *Diagnostic and Statistical Manual of Mental Disorders*, or the Research Diagnostic Criteria
- Acute treatment (at least six weeks duration) or long term treatment (at least six months (relapse) or 12 months (recurrence)) for prevention of relapse or recurrence
- Comparison of reboxetine with placebo or any antidepressant (including St John's wort); treatment according to approval status in Germany
- Evaluation of at least one prespecified patient relevant outcome (in this context, the term "patient relevant" refers to "how a patient feels, functions, or survives"[16])
- Publication in English, German, or French (or any other language if the trial was classified as potentially relevant according to the English title or abstract)
- Availability of a full text document (for example, journal article or clinical study report).

This publication is limited to acute treatment trials of reboxetine versus placebo or SSRIs. The outcomes presented are restricted to the most commonly reported outcomes in depression trials. Benefit outcomes were remission and response rates. Harm outcomes were rates of patients with at least one adverse event (any adverse event according to the definitions used in the primary trials) and rates of withdrawals owing to adverse events (any adverse event according to the definitions used in the primary trials). Harms were further described by the overall rates of patients with serious adverse events (any serious adverse event according to the definitions used in the primary trials).

According to the review protocol, response and remission data were analysed on the basis of the definitions and instruments used in the primary trials. All trials applied the Hamilton depression rating scale and 10 trials additionally applied the Montgomery-Åsberg depression rating scale. We primarily considered the response and remission outcomes on the Hamilton depression rating scale. In all trials, response was defined as a reduction in the score on the Hamilton depression rating scale of 50% or more from baseline to end of study, and remission was defined as a reduction in the score on the Hamilton depression rating scale to below an absolute threshold at end of study (score $\leq$10 in all trials except in one trial where the score threshold was $\leq$8).

Search strategy and study selection

We searched for relevant primary and secondary publications (systematic reviews and health technology assessment reports) in Medline, Embase, PsycINFO, BIOSIS, and the Cochrane Library published up until February 2009. The full search strategy, including the search terms used for the various databases, has been described elsewhere.[12]

We scrutinised the reference lists of the primary and secondary publications retrieved to identify further trials. In addition, clinical trial registries and trial results databases available on the internet were screened, as were the websites of the European Medicines Agency and the US Food and Drug Administration.

In order to obtain the most complete dataset possible, we asked the manufacturer of reboxetine (Pfizer) to supply unpublished trials and additional unpublished data from published trials. As a prerequisite for the use of unpublished data, IQWiG asked the manufacturer to sign an agreement requiring: (1) submission of a list of all sponsored published and unpublished trials investigating reboxetine; (2) submission of documents (generally the clinical study reports) compliant with the CONSORT criteria for all relevant trials selected by IQWiG; and (3) permission for publication of all previously unpublished relevant data. This procedure was required to avoid bias through selective provision of data. Finally, people and parties who had submitted comments on the preliminary version of the health technology assessment report at the public hearing in July 2009 were asked to provide any additional relevant trials.

Two reviewers independently screened titles and abstracts of the retrieved citations to identify potentially eligible primary and secondary publications. In a first broad screening step, citations were excluded if clearly irrelevant; that is, if a primary publication was not a clinical trial in humans with depression, or if a secondary publication of eligible trials was not a systematic review. In a second screening step, the full set of eligibility criteria was applied. Potentially relevant articles were then screened as full texts. Disagreement was resolved by consensus.

Data extraction and assessment of risk of bias

The individual steps of the data extraction and assessment of risk of bias were always conducted by one person and checked by another. Details of the trials were extracted using standardised tables. Information and data from publications were supplemented by clinical study reports provided by the manufacturer. We always extracted data from the intention to treat populations. Clinical study reports were always considered the primary source in instances of conflict with the publication. Disagreement was resolved by consensus.

Information was extracted from each included trial on:

- Study characteristics, including citation, study design, setting (inpatient or outpatient), inclusion and exclusion criteria, length of follow-up, sample size, location, number of centres, and year of completion
- Characteristics of the study participants, including age, gender, and disease severity at baseline
- Characteristics of the test and control interventions, including dose
- Outcomes and type of outcome measures (outcomes as presented above; measurement tools as used in the individual trials)
- Risk of bias items.

The risk of bias at the study level was assessed on the basis of the adequacy of the following

criteria: randomisation; allocation concealment; blinding of patients and investigators; and complete and non-selective results reporting. The risk of bias at the outcome level was assessed on the basis of the adequacy of: application of the intention to treat principle; blinding of the outcome assessor; statistical evaluation; and complete and non-selective results reporting. Trials and outcomes were categorised into those with a low risk of bias and those with a high risk.

Data analysis

If feasible and meaningful, data were pooled by means of meta-analyses. Effect measures were reported as odds ratios (ORs) and 95% confidence intervals (CIs) for binary data. A random effects model was used to calculate a pooled effect estimate. Statistical significance was assumed for $P<0.05$. Heterogeneity of effect sizes was assessed by using the I^2 statistic; pooled estimates were not calculated if substantial heterogeneity was observed ($I^2>50\%$). If heterogeneity with $I^2>50\%$ was shown, sensitivity analyses were conducted, when appropriate, to assess possible sources of heterogeneity across the trials included. The review protocol prespecified potential effect modifiers, including gender and trial setting (inpatient or outpatient). These factors were investigated by means of random effects meta-regression analyses based on aggregate study data.[17]

To assess publication bias, effect sizes in the published, unpublished, and overall dataset were compared. In addition, the differences in effect sizes between published and unpublished data, and between published and overall data, were expressed as the ratio of odds ratios (ROR). The magnitude of the overestimation or underestimation of effect sizes in published versus overall data (publication bias) was expressed as percentage changes.

Meta-analyses were performed using SAS version 9.1.3. If meta-analyses were not possible, the results of the individual trials were assessed.

Results

Study selection

The process of study selection is presented in figure 1⇓. The search in bibliographic databases yielded 2596 citations, of which 713 were classified as potentially relevant and subjected to strict eligibility assessment. A total of 13 citations (10 trials) met the inclusion criteria; however, two of these 13 citations were publications on subgroups of otherwise unpublished trials,[18] [19] and one was the only available publication on the total population being studied but did not report the main outcomes.[20] In the assessment of publication bias, we considered these three trials to be "unpublished." No trials were identified in clinical trial or trial results registries or in the European Medicines Agency or FDA websites.

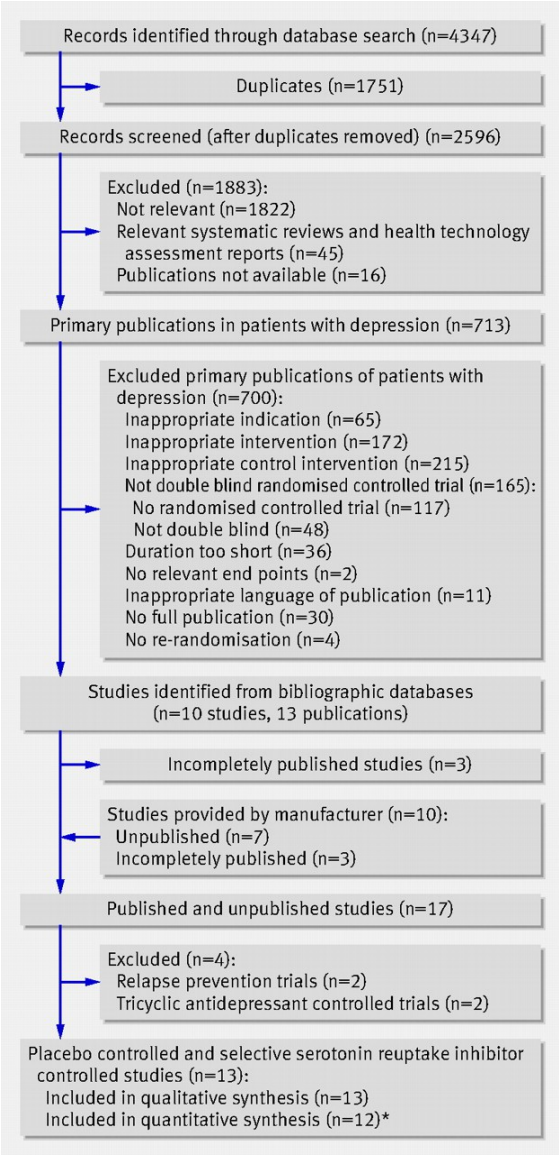

Fig 1 Flowchart of study selection. *Excluding long term acute treatment trial

The retrieval of previously unpublished trials was hampered by the fact that during preparation of the preliminary health technology assessment report, the manufacturer of reboxetine did not provide a complete list of unpublished trials as requested by IQWiG.[21] [22] Secondary publications clearly indicated that further potentially relevant unpublished trials existed.[6] [8] As the preliminary report showed that reboxetine had been tested in at least 16 trials including about 4600 patients, but data on almost two thirds of these patients were not accessible, the institute initially concluded that no meaningful assessment of reboxetine was possible.[21] [22]

After the publication of the preliminary report, the manufacturer decided to cooperate and provided most of the missing data (one venlafaxine controlled trial[23] was not available as a full publication). Thus, an additional 10 previously unpublished or incompletely published reboxetine trials were considered in the final health technology assessment report.[12] Two trials with tricyclic antidepressants as active controls and two relapse prevention trials were excluded from the present analysis.

Of the remaining 13 eligible acute treatment trials, three were placebo controlled, five were active controlled, and five had both placebo and active controlled arms (one of which had a tricyclic antidepressant arm that was not considered). A total of 4098 patients were analysed: 2256 in the

reboxetine versus placebo comparisons and 2641 in the reboxetine versus SSRI comparisons.

Study characteristics

The characteristics of the pool of 13 acute treatment trials that were placebo controlled, SSRI controlled, or both are presented in tables 1 and 2⇓ ⇓. All trials were sponsored by predecessors of Pfizer (Pharmacia, and Pharmacia & Upjohn), except for Berlanga and Flores-Ramos 2006 (sponsored by Lundbeck), and included adult patients with major depressive disorder according to the third edition, revised or the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders*. In the four fluoxetine controlled trials and in one citalopram controlled trial, the SSRIs were potentially underdosed compared with reboxetine (according to doses standardised on the basis of the maximum approved dose; see table 2). The trials were well balanced between treatment arms with respect to patient baseline characteristics.

Table 1 Trial publication details

Trial	Year of completion	Primary publication available?	Clinical study report available?*
014	Before 1996	Refs 42-44	Ref 45†
015	1992	None, only a pooled analysis (ref 6)	Ref 46
016	1993	Ref 47	Ref 48
032	2001	None	Ref 49
043	2001	Ref 50	Ref 51
045	1999	None	Ref 52
046	2000	None	Ref 53
047	2000	Ref 19, although the data for the full study population were not reported	Ref 54
049	1998	None	Ref 55
050	1999	Ref 56	
052	2000	Ref 18, although the data for the full study population were not reported	Ref 57
091	1990	Refs 58 and 59	Ref 60
Berlanga and Flores-Ramos 2006	2003	Ref 61	No

*As a matter of principle, the German Institute for Quality and Efficiency in Health Care requests documents compliant with the CONSORT criteria from manufacturers on all relevant trials selected. If cooperative, manufacturers usually provide the full clinical study report; that is, a written description of the study that follows the guidelines of the International Conference on Harmonisation.[62]

†Only addendum.

Table 2 Trial characteristics and baseline demographics

							Baseline demographi		
Treatments	**Dose (mg/d)**	**Proportion of maximum approved daily dose (%)**	**Number of patients randomised**	**Duration of active medication (weeks)**	**Number of centres (locations)***	**Setting**	**Age (mean (SD))**	**Proportion female (%)**	**Ham depre rati scal (me (SI**
Reboxetine	8-10	67-83	126	8	33 (Europe, South America)	Inpatient and outpatient	40 (12)	67	26.8
Fluoxetine	20-40	25-50	127				40 (12)	65	26.9
Placebo	—	—	128				44 (12)	54	27.4
Reboxetine	8-10	67-83	112	6	34 (North America, Europe, Australia)	Inpatient and outpatient	46 (13)	63	27.5
Imipramine	150-200	Inpatient: 50-67 Outpatient: 100-133	115				44 (11)	67	26.9
Placebo	—	—	112				43 (12)	48	27.1
Reboxetine	8-10	67-83	79	8	16 (Europe, South America, Australia)	Inpatient and outpatient	44 (13)	72	28.6
Fluoxetine	20-40	25-50	89				44 (12)	72	27.4
Reboxetine	8-10	67-83	43	8	5 (Asia)	Inpatient and outpatient	41 (15)	63	27.2
Fluoxetine	20-40	25-50	42				36 (13)	62	28.3
Reboxetine	8-10	67-83	183	24	23 (Europe)	Outpatient	43 (13)	69	27.4
Citalopram	20-40	33-67	176				42 (12)	60	27.4
Reboxetine	8	67	89	6	48 (Europe, Asia)	Inpatient and outpatient	42 (11)	63	26.4
Placebo	—	—	87				41 (11)	70	26.4
Reboxetine	8-10	67-83	265	8	94 (North America)	N/A	40 (11)	71	23.0
Paroxetine	20-40	40-80	265				40 (12)	69	22.8
Placebo	—	—	257				39 (12)	70	23.0
Reboxetine	8-10	67-83	258	8	68 (North America)	N/A	39 (12)	74	24.2

							Baseline demographi		
Treatments	Dose (mg/d)	Proportion of maximum approved daily dose (%)	Number of patients randomised	Duration of active medication (weeks)	Number of centres (locations)*	Setting	Age (mean (SD))	Proportion female (%)	Ham depre rati scal (me (SI
Paroxetine	20-40	40-80	262				40 (11)	72	23.9
Placebo	—	—	254				37 (11)	82	23.7
Reboxetine	8-10	67-83	107	6	9 (North America)	Outpatient	40 (12)	55	25.1
Placebo	—	—	105				40 (11)	58	25.3
Reboxetine	8-10	67-83	150	8	24 (North America)	Outpatient	40 (11)	63	25.6
Fluoxetine	20-40	25-50	150				41 (11)	66	26.0
Placebo			150				40 (11)	60	25.5
Reboxetine	8-10	67-83	159	8	41 (Europe)	N/A	42 (12)	63	24.2
Paroxetine	20-40	40-80	166				45 (11)	62	24.1
Reboxetine	10	83	28	6	3 (North America, South America)	Inpatient	42 (N/A)	46	35.7 (
Placebo	—	—	28				40 (N/A)	50	35.1 (
Reboxetine	4-8	33-67	46	8	1 (Central America)	Outpatient	N/A	N/A	N/
Citalopram	20-40	33-67	55				N/A	N/A	N/

*Details on individual countries are provided in web table A.

†To comply with the intention to treat principle, missing data from discontinued patients were imputed by using the last observation carried forward method.

N/A, not available.

There were no major differences between trials in terms of dosage and mean patient age. However, there were differences in setting (inpatient, outpatient, or both) and baseline severity of depression as measured by the Hamilton depression rating scale. For more details on trial characteristics see web table A.

Risk of bias

The overall methodological quality of the trials was good (table 3⇓). At the trial level, the risk of bias was low in all but one study, which had a high risk of bias at the trial level owing to unclear allocation concealment and blinding. At the outcome level, the risk of bias was low for all four benefit and harm outcomes in nine out of the 13 trials. Three trials had a high risk of bias at the outcome level owing to an inadequate intention to treat analysis. Analyses excluding the outcomes

at high risk of bias did not alter the conclusions (data not shown). As no clear dose-response relationship has been shown for fluoxetine and citalopram,[24] [25] the potential underdosing of these agents in five trials did not affect the risk of bias.

Table 3 Risk of bias

Trial	Risk of bias: trial level	Risk of bias: outcome level			
		Remission	Response	Adverse events	Withdrawals owing to adverse events
014	High*	High†	High†	High†	High†
015	Low	Low	Low	Low	Low
016	Low	Low	Low	Low	Low
032	Low	High‡	High‡	Low	Low
043	Low	High‡	High‡	Low	Low
045	Low	Low	Low	Low	Low
046	Low	Low	Low	Low	Low
047	Low	Low	Low	Low	Low
049	Low	Low	Low	Low	Low
050	Low	Low	Low	Low	Low
052	Low	Low	Low	Low	Low
091	Low	Low	Low	Low	Low
Berlanga and Flores-Ramos 2006	Low	High‡	High‡	No data	No data

*High because of unclear randomisation, allocation concealment, and blinding.

†High because of high risk of bias at trial level.

‡High because of violation of the intention to treat principle.

Owing to the availability of a comprehensive set of the relevant data on reboxetine versus placebo and SSRIs, the risk of publication bias on the results of the final analysis was minor.

Effects of interventions

In this text, the terms “superior” and “inferior” refer to statistically significant differences between treatment groups ($P<0.05$).

Meta-analyses of remission and response rates

The Hamilton depression rating scale was used in the meta-analyses of remission and response rates. No statistically significant difference between reboxetine and placebo was noted in the meta-analysis of remission rates (OR 1.17, 95% CI 0.91 to 1.51; P=0.216; fig 2⇓).

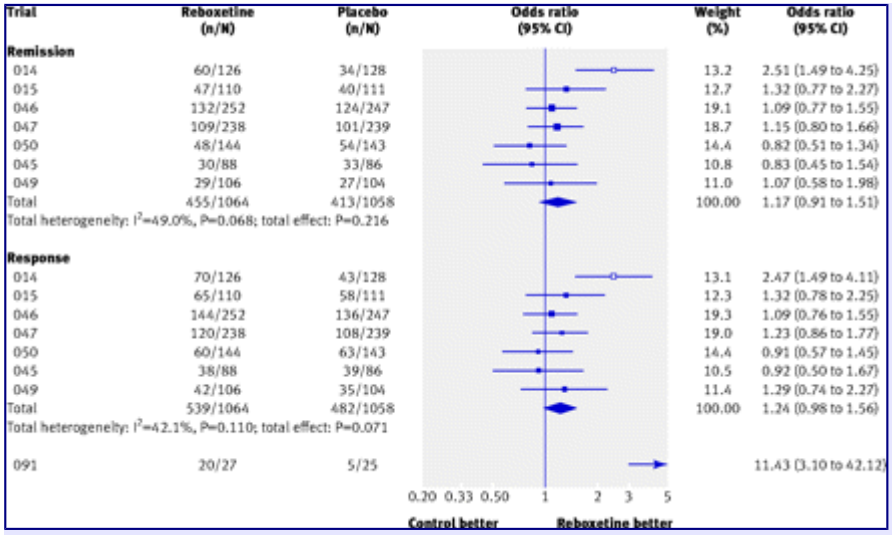

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Fig 2 Forest plot showing meta-analyses of remission and response rates for trials that compared reboxetine with placebo. Empty boxes show published studies and filled boxes show unpublished studies. Study 091 is not included in the pooled analysis of response of reboxetine versus placebo because of high heterogeneity (see text for details). CI, confidence interval; n, number of patients with event; N, number of patients in treatment group

Substantial heterogeneity (I^2=67.3%; p=0.003) was shown in the meta-analysis of response rates including all eight trials that compared reboxetine with placebo, and consequently no point estimate was calculated. The only known inpatient trial—trial 091 (n=52), which had an OR of 11.43 (95% CI 3.10 to 42.12)—was obviously a statistical outlier (figure 2).

In the sensitivity analysis using meta-regression analysis, setting had an effect on the outcome response. Patients who received reboxetine in an inpatient setting were more likely to show a good response compared with placebo than were patients who received reboxetine in an outpatient setting (P=0.001 inpatients *v* outpatients; trials 091 *v* 049 and 050). In a second scenario, the proportion of inpatients was used as the independent variable. This analysis also included trials 014 and 015, for which the proportion of inpatients was available from Montgomery et al 2003.7 This scenario confirmed the influence of setting (P<0.001). The meta-analysis of response rates in the outpatient only trials (049 and 050) showed no statistically significant difference between reboxetine and placebo (OR 1.05, 95% CI 0.73 to 1.50; P=0.796 I^2=0%). These findings indicate that patient setting was the most probable effect modifier. After exclusion of trial 091, the meta-analysis of response rates in the seven remaining trials showed no statistically significant difference between reboxetine and placebo (OR 1.24, 95% CI 0.98 to 1.56, P=0.071, I^2=42.1%; figure 2).

Reboxetine was inferior to SSRIs in the meta-analysis of remission rates (OR 0.80, 95% CI 0.67 to 0.96; P=0.015; fig 3⇓). A similar, although non-significant, trend in remission rates was shown when reboxetine was compared with the individual SSRIs (fluoxetine, paroxetine, and citalopram). However, if remission rates according to the Montgomery-Åsberg depression rating scale rather than the Hamilton depression rating scale were analysed from trials using this instrument as the primary scale (trials 046 and 047), reboxetine was inferior to paroxetine (OR 0.72, 95% CI 0.56 to 0.93). In the long term acute treatment trial (trial 043), reboxetine was inferior to citalopram (OR 0.51, 95% CI 0.32 to 0.83). However, the intention to treat principle was violated in this trial, so a worst case analysis was conducted in which the difference in remission rate compared with citalopram was no longer statistically significant.

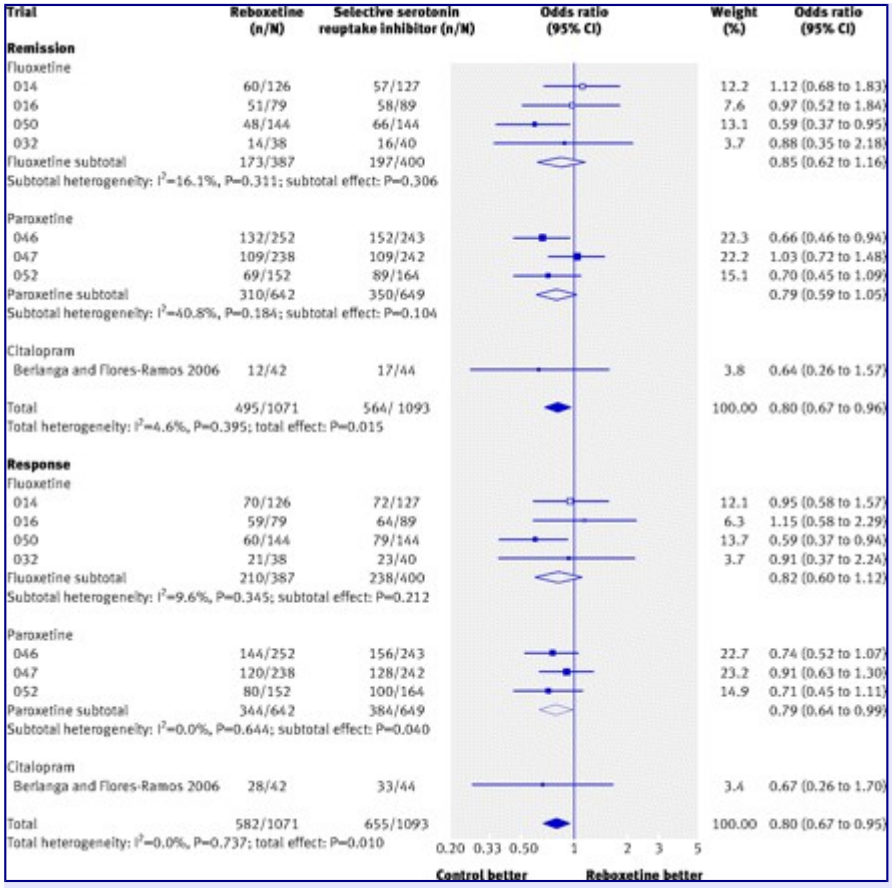

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Fig 3 Forest plot showing meta-analyses of remission and response rates for trials that compared reboxetine with selective serotonin reuptake inhibitors (SSRIs; fluoxetine, paroxetine, and citalopram). Empty boxes show published studies and filled boxes show unpublished studies. Empty diamonds show subtotals (individual SSRIs) and filled diamonds show overall totals (all SSRIs). CI, confidence interval; n, number of patients with event; N, number of patients in treatment group

Reboxetine was also inferior to SSRIs in the meta-analysis of response rates (OR 0.80, 95% CI 0.67 to 0.95; P=0.010). A similar trend was shown when reboxetine was compared with the individual SSRIs, where the trend reached statistical significance in the comparison of reboxetine and paroxetine (OR 0.79, 95% CI 0.64 to 0.99; P=0.04). In the long term acute treatment trial, no statistically significant difference was shown between reboxetine and citalopram (OR 0.60, 95% CI 0.35 to 1.03).

The overall findings were also reflected in the subset of trials that were both placebo controlled and SSRI controlled (n=4), which are suited to demonstrating assay sensitivity. The SSRIs were superior to placebo and reboxetine in this analysis, but no statistically significant difference was shown between reboxetine and placebo (see web figure A).

Meta-analyses of adverse events and withdrawals owing to adverse events

Reboxetine was inferior to placebo (that is, it was associated with higher event rates) in the meta-analyses of the rates of patients with at least one adverse event and in the meta-analysis of the rates of withdrawals owing to adverse events (OR 2.14, 95% CI 1.59 to 2.88; P<0.001 and OR 2.21, 95% CI 1.45 to 3.37; P<0.001, respectively; fig 4⇓).

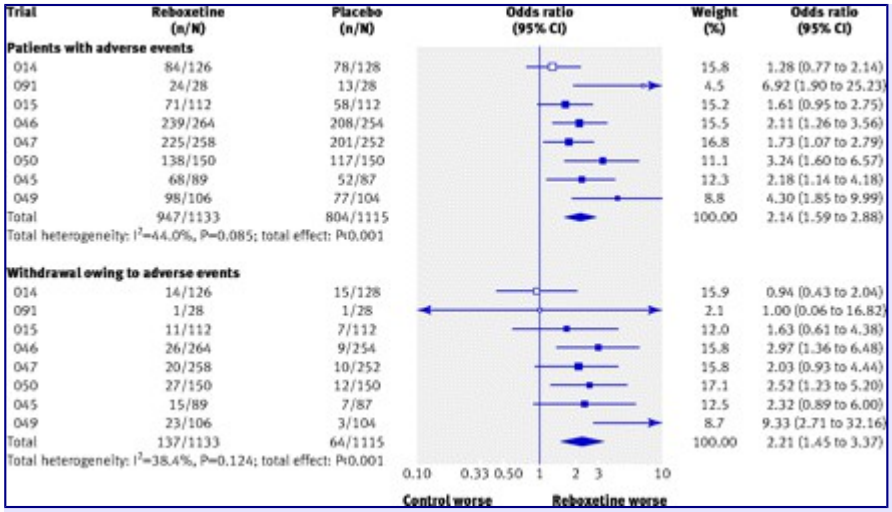

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Fig 4 Forest plot showing meta-analyses of rates of patients with at least one adverse event and rates of withdrawals owing to adverse events for trials that compared reboxetine with placebo. Empty boxes show published studies and filled boxes show unpublished studies. CI, confidence interval; n, number of patients with event; N, number of patients in treatment group

The rates of patients with at least one adverse event did not differ significantly between patients treated with reboxetine and those who received an SSRI (OR 1.06, 95% CI 0.82 to 1.36; P=0.667; fig 5⇓). The same finding was seen for patients on reboxetine versus those treated with individual SSRIs. A meta-regression analysis showed a gender effect in the comparison of reboxetine with fluoxetine (P=0.022 for the interaction test): in men reboxetine was inferior to fluoxetine in the meta-analysis of patients with at least one adverse event (OR 2.76, 95% CI 1.28 to 5.93), whereas no significant difference was shown in women (OR 0.90, 95% CI 0.51 to 1.59). In the long term acute treatment trial, reboxetine was inferior to citalopram (OR 1.57, 95% CI 1.03 to 2.38).

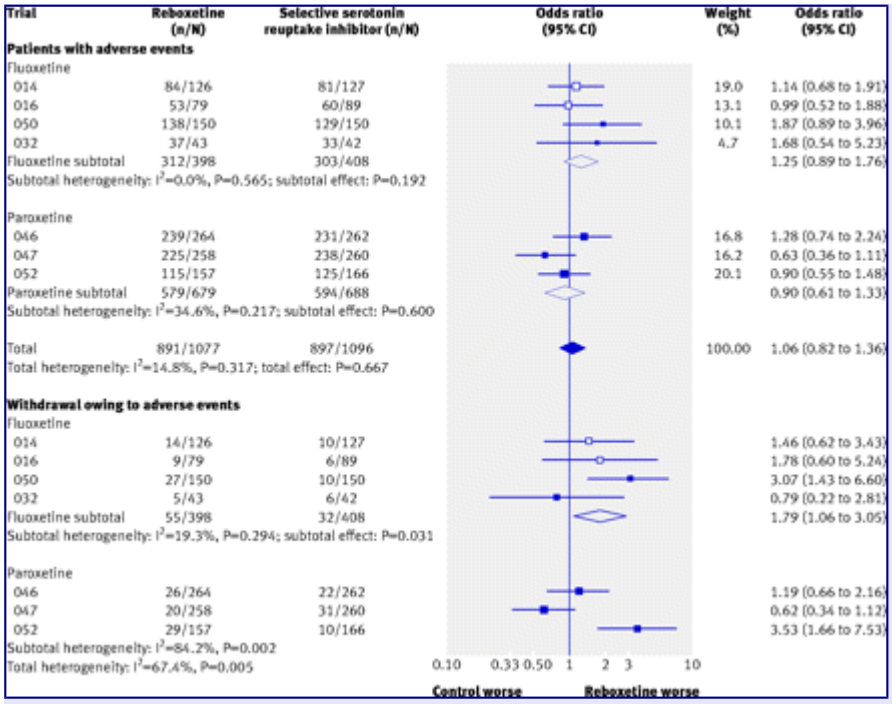

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Fig 5 Forest plot showing meta-analyses of rates of patients with at least one adverse event and rates of withdrawals owing to adverse events for trials that compared reboxetine with selective

serotonin reuptake inhibitors (SSRIs; fluoxetine and paroxetine). Empty boxes show published studies and filled boxes show unpublished studies. Empty diamonds show subtotals (individual SSRIs) and filled diamonds show overall totals (all SSRIs). CI, confidence interval; n, number of patients with event; N, number of patients in treatment group

Substantial heterogeneity (I^2=67.4%) was shown in the meta-analysis of the rates of withdrawals owing to adverse events in the comparison between reboxetine and SSRIs, which was in part owing to variations in the results of the individual SSRIs. The comparison between reboxetine and fluoxetine showed low heterogeneity (I^2=19.3%) and statistically significantly more withdrawals owing to adverse events for reboxetine (OR 1.79, 95% CI 1.06 to 3.05; P=0.031). On the other hand, the comparison between reboxetine and paroxetine showed substantial heterogeneity (I^2=84.2%), but the sensitivity analysis did not identify a potential effect modifier. We therefore concluded that there was no proof of a difference between reboxetine and paroxetine concerning rates of withdrawals owing to adverse events. In the long term acute treatment trial, reboxetine was inferior to citalopram (OR 4.61, 95% CI 2.15 to 9.89).

Further information on adverse events

The rates of serious adverse events (including events related to suicide) were low and did not differ significantly between reboxetine and placebo or reboxetine and SSRIs (data on overall serious adverse events not shown). A total of 18 serious adverse events related to suicide (suicidal tendencies, suicide attempts, or completed suicides) were noted (six for reboxetine; four for placebo; eight for SSRIs). One death (a completed suicide under placebo) was reported, which was the only mortality in the study arms investigated. However, with respect to study design and duration, none of the trials were aimed at investigating suicide related events or overall mortality. The validity of the results of these outcomes is therefore limited and the data do not provide clarification.

Publication bias

A substantial proportion of patient data (74%) had not been previously published: 86% (1946/2256 patients) in the comparisons of reboxetine and placebo and 67% (1760/2641 patients) in the comparisons of reboxetine and SSRIs (table 1⇑).

For both benefit outcomes, the addition of unpublished data changed the superiority of reboxetine versus placebo shown in published data to a non-significant difference and also changed the non-significant difference between reboxetine and SSRIs to an inferiority of reboxetine (fig 6⇓). Comparison of the published data with the full dataset (published and unpublished) showed that the published data overestimated the beneficial effect of reboxetine compared with placebo by 99-115% and of reboxetine compared with SSRIs by 19-23%.

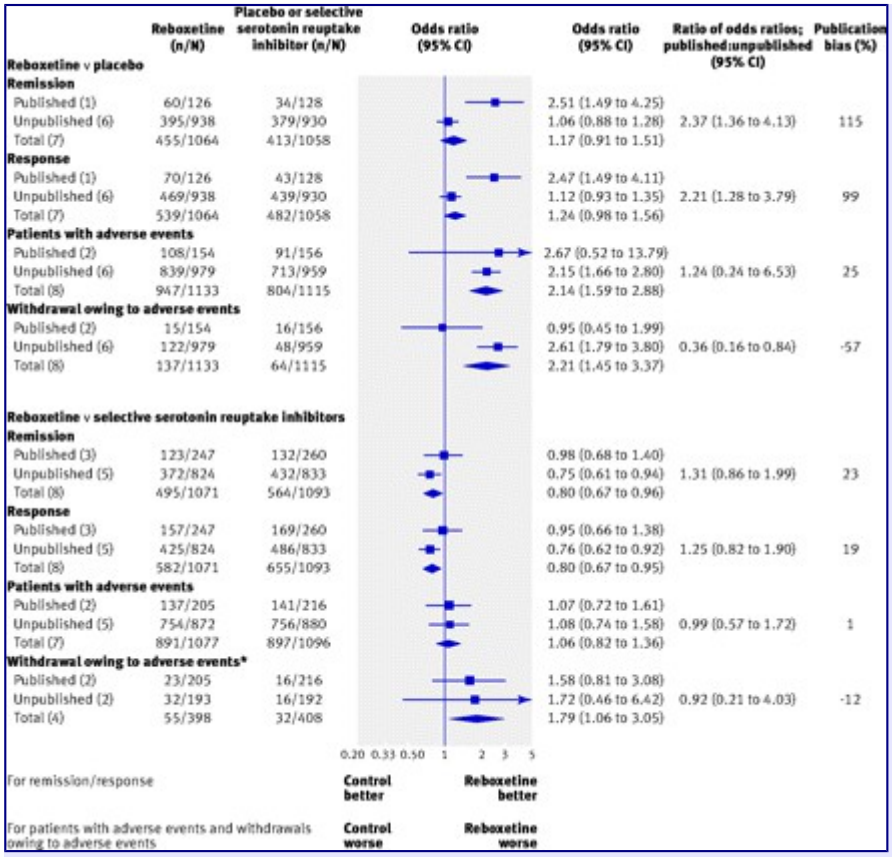

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Fig 6 Forest plot showing meta-analyses of published, unpublished, and all trials. Publication bias (right column) is presented as the ratio of odds ratios of published results versus overall results. The extent of publication bias is expressed as percentage change between the analysis of published trials only and the analysis of all trials (that is, publication bias=$100\times(OR_{\text{published data}}/OR_{\text{total data}}-1)$).

*Fluoxetine controlled studies only

For both harm outcomes, the addition of unpublished data changed the non-significant difference between reboxetine and placebo shown in published data to an inferiority of reboxetine. For rates of withdrawals owing to adverse events, the addition of unpublished data changed the non-significant difference between reboxetine and fluoxetine to an inferiority of reboxetine; this was primarily owing to the increased power of the analysis rather than to major differences in withdrawal rates between published and unpublished data. For patients with at least one adverse event, no significant impact of unpublished data was shown in the comparison between reboxetine and SSRIs.

Discussion

To our knowledge, this is the first systematic review of a comprehensive evidence base of published and unpublished acute treatment trials of reboxetine versus placebo or SSRIs in adults with major depressive disorder. We found that, overall, reboxetine was ineffective as an antidepressant because it showed no benefit over placebo and was inferior to SSRIs for remission and response rates. A benefit of reboxetine (higher response rates) was shown in a placebo controlled trial in inpatients; however, this trial was too small to draw general conclusions on the effect of reboxetine in this patient population. Reboxetine was inferior to placebo for both harm outcomes and to fluoxetine for rates of withdrawals owing to adverse events.

Given the potential underdosing of fluoxetine and citalopram in five trials, our findings on

reboxetine might be considered conservative. At the same time, the advantages of SSRIs concerning harm might be overestimated. However, as stated, no clear dose-response relationship has been shown for fluoxetine and citalopram.[24] [25] Furthermore, in our test of assay sensitivity that included two of the four potentially underdosed fluoxetine arms, even the lower fluoxetine dose showed a clear benefit compared with placebo (OR 1.98, 95% CI 1.19 to 3.28, I^2=53.8%), thus qualifying the effect of dosing in treatment for depression.

Data on 74% of the patients included in our analysis was unpublished, indicating that the published evidence on reboxetine so far has been severely affected by publication bias. Our comparison of published and unpublished trials confirmed this assumption: the positive benefit-risk ratio of reboxetine in the published literature was changed to a negative ratio if unpublished trials were added to the analysis.

Comparison with other reviews

The results of our review largely contradict the findings of previous systematic reviews and analyses of reboxetine versus placebo[6] [7] [9] and reboxetine versus active comparators.[8] [9] [11]

The solely placebo controlled analyses by Ferguson et al[6] and Montgomery et al[7] both found greater efficacy (including higher response rates) for reboxetine compared with placebo, and Ferguson et al also found comparable harms. However, both reviews included only three of the eight studies considered in our review (plus the inpatient trial by Ban et al 1998[26]). These two reviews also included only one unpublished trial (015), even though the relevant unpublished trials had been completed before publication of these analyses and both reviews were cowritten by a sponsor employee. The meta-analysis by Chuluunkhuu et al[9] concluded that reboxetine showed superior efficacy to placebo and found no difference in efficacy of reboxetine compared with SSRIs and other antidepressants. However, this analysis considered only published data.

Although the meta-analysis by Papakostas et al[8] identified and included a large body of unpublished studies that used SSRIs as the control (the same set as we used), they found no significant difference in response rates between SSRIs and reboxetine (risk ratio 1.08, 95% CI 0.98 to 1.19). Their analysis included the long term acute treatment trial 043, which we analysed separately. In contrast, our analysis showed that reboxetine was inferior to SSRIs, even if trial 043 was included (recalculated according to Papakostas: risk ratio (SSRI *v* reboxetine) 1.10, 95% CI 1.03 to 1.17; P=0.003). The reason for this discrepancy is unclear, because Papakostas et al reported only point estimates and CIs and did not report the number of actual events or the corresponding populations.

The widely discussed systematic review by Cipriani et al,[11] which assessed 12 new generation antidepressants in a network meta-analysis and ranked reboxetine last, had similar findings to those of our review. These authors found significantly lower response rates for reboxetine than for all SSRIs investigated, as well as significantly higher dropout rates versus fluoxetine, citalopram, escitalopram, and sertraline. However, despite the similarity in findings, the evidence base of the Cipriani review differed markedly from that in our review because placebo controlled trials were omitted and trials that were not double blind, which carry a higher risk of bias, were considered. In addition, unpublished trials of reboxetine on file at the manufacturers were not considered, even though significant publication bias has been shown in antidepressant research. Given the sources of bias noted, the results of the Cipriani review should be interpreted with caution.

Our findings that reboxetine was superior (higher response rates) to placebo in a small trial in inpatients and that patient setting was a probable effect modifier are supported by the four week active controlled and placebo controlled inpatient trial by Ban et al[26] (n=169 in the reboxetine and placebo arms), which we excluded owing to its short duration. Ban et al also found a statistically

significant higher response rate in inpatients who received reboxetine compared with those who received placebo (60% *v* 35%; OR 2.70, 95% CI 1.45 to 5.03 (own calculation)).

Strengths and limitations of the review

The main strength of our review is the inclusion of a large amount of previously unpublished data. As we made extensive efforts to identify unpublished trials, we are optimistic that we analysed the vast majority or even all of the placebo controlled and SSRI controlled double blind randomised trials of reboxetine in adults with major depression.

Our review also has a number of limitations. We only had access to aggregated data. To assess the impact of effect modifiers, meta-analysis of individual patient data would be needed to determine the setting in studies with mixed settings and to test our hypothesis that the setting was the effect modifier explaining the substantial heterogeneity in the meta-analysis of response rates in placebo controlled trials.

Our results are further limited by the fact that they only refer to acute treatment trials, only one of which lasted more than eight weeks. However, six to eight weeks is the standard study duration in trials investigating the acute treatment of depression. The long term acute treatment trial showed similar, though not always statistically significant, trends to the short term trials. Other long term outcomes in depression, such as prevention of relapse or recurrence, were not the focus of this paper.

Finally, except for a subgroup analysis for gender and setting, we assessed total populations of patients with major depressive disorder. No analyses were performed in other subgroups of patients (for example, patients with severe disease or specific major depressive disorder symptoms such as anxiety or cognitive impairment), in which treatment effects may differ.

Publication bias

Our difficulties in retrieving unpublished trial data and our results of the comparison between published and previously unpublished trials are a further example of publication bias, a problem that has been known in clinical research for decades.[27] [28] [29] [30] [31] A recent narrative review has shown that publication bias affects a wide range of medical indications and interventions.[32] Such bias, including industry sponsorship bias, has frequently been identified in research on antidepressants (table 4⇓). For example, Turner et al[33] published a comparison of FDA reviews of placebo controlled antidepressant trials and matching publications, which showed that, overall, published trials overestimated effect sizes by 32% (11 to 69% for individual agents); the estimates in our review were even higher. Whittington et al[34] investigated SSRIs in the treatment of childhood depression and found that the addition of unpublished data reversed the benefit-risk profile for all but one SSRI.

Table 4 Examples of publication bias and industry sponsorship bias in trials of antidepressants

Source	Study type	Antidepressant type	Findings
Turner et al 2008[33]	Comparison of FDA reviews and matching publications	SSRIs, SNRIs, NDRIs, TeCAs, and atypical antidepressants	"Among 74 FDA registered studies, 31%, accounting for 3449 study participants, were not published . . . A total of 37 studies viewed by the FDA as having positive results were published . . . Studies viewed by the FDA as having negative or questionable results were, with 3 exceptions,

Source	Study type	Antidepressant type	Findings
			either not published (22 studies) or published in a way that, in our opinion, conveyed a positive outcome (11 studies). According to the published literature, it appeared that 94% of the trials conducted were positive. By contrast, the FDA analysis showed that 51% were positive . . . the increase in effect size ranged from 11% to 69% for individual drugs and was 32% overall."
Kirsch et al 2008[63]	Meta-analysis of data submitted to the FDA	SSRIs, SNRIs, and atypical antidepressants	"[T]he FDA public disclosure did not include mean changes for nine trials that were deemed adequate and well controlled but that failed to achieve a statistically significant benefit for drug over placebo . . . Specifically, four sertraline trials involving 486 participants and one citalopram trial involving 274 participants were reported as having failed to achieve a statistically significant drug effect, without reporting mean Hamilton rating scale of depression scores. We were unable to find data from these trials on pharmaceutical company websites or through our search of the published literature. These omissions represent 38% of patients in sertraline trials and 23% of patients in citalopram trials."
Whittington et al 2004[34]	Systematic review of published versus unpublished data	SSRIs and SNRIs	"Data for two published trials suggest that fluoxetine has a favourable risk-benefit profile, and unpublished data lend support to this finding. Published results from one trial of paroxetine and two trials of sertraline suggest equivocal or weak positive risk-benefit profiles. However, in both cases, addition of unpublished data indicates that risks outweigh benefits. Data from unpublished trials of citalopram and venlafaxine show unfavourable risk-benefit profiles."
Melander et al 2003[38]	Analysis of industry sponsored studies in new drug applications	SSRIs	"Multiple publication: 21 studies contributed to at least two publications each, and three studies contributed to five publications. Selective publication: studies showing significant effects of drug were published as stand alone publications more often than studies with non-significant results. Selective reporting: many publications ignored the results of intention to treat analyses and reported the more favourable per protocol analyses only."
Jureidini et	Case report on	Paroxetine	"The published report of study 329 of paroxetine

Source	Study type	Antidepressant type	Findings
al 2008[64]	selective reporting		in adolescents sponsored by GlaxoSmithKline claims that 'paroxetine is generally well tolerated and effective for major depression in adolescents.' By contrast, documents obtained during litigation reveal that study 329 was negative for efficacy on all eight protocol specified outcomes and positive for harm."
Tungaraza et al 2007[65]	Analysis of influence of industry authorship and funding	Not specified*	"Independent studies were more likely to report negative findings than were industry funded studies. However, the involvement of a drug company employee had a much greater effect on study outcome than financial sponsorship alone."
Perlis et al 2005[66]	Analysis of influence of industry funding and financial conflict of interest	Not specified*	"Among the 162 randomised, double blind, placebo controlled studies examined, those that reported conflict of interest were 4.9 times more likely to report positive results; this association was significant only among the subset of pharmaceutical industry funded studies."
Kelly et al 2006[67]	Analysis of influence of industry funding	Not specified*	"Favourable outcomes were significantly more common in studies sponsored by the drug manufacturer (78%) than in studies without industry sponsorship (48%) or sponsored by a competitor (28%)."

*Findings also refer to other psychiatric drugs. All analyses examined drug trials reported in psychiatric journals. No separate results for antidepressants were reported.

FDA, Food and Drug Administration; NDA, new drug application; NDRI, norepinephrine and dopamine reuptake inhibitor; SNRI, serotonin and norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TeCA, tetracyclic antidepressant.

In addition to publication bias, outcome reporting bias has been identified as a major problem in the reporting of clinical trials, resulting in a distorted public record of an intervention.[35] [36] [37] [38] Our review also identified this type of bias—for three reboxetine trials, only results on subpopulations or selected outcomes were available in the published literature (trials 047, 050, 052; table 1⇑).

The more positive benefit-risk ratio in published data compared with unpublished data also affects the content of clinical guidelines. For example, the National Institute for Health and Clinical Excellence (NICE) guideline on the treatment and management of depression in adults is based on published studies of reboxetine, and concludes that "Reboxetine is superior to placebo and as effective as other antidepressants in the treatment of depression."[10] In our opinion, this conclusion can no longer be upheld.

The ongoing problem of publication bias shows that unbiased decision making in health care requires mandatory public disclosure of all clinical trial data. The US FDA Amendments Act of 2007[39] solves the problem in part by requiring protocol information and study results for clinical trials to be made public on the clinicaltrials.gov website (www.clinicaltrials.gov; please see accompanying comment (doi:10.1136/bmj.c4942) for further details). Similar legislation is also being introduced in Europe, with the mandatory public disclosure of data from the clinical trials database EudraCT (eudract.ema.europa.eu),[40] [41] but the date of implementation is not yet clear.

As the full assessment reports on reboxetine prepared by regulatory authorities are not publicly available, it is not clear as to how the comprehensive body of evidence (including that on efficacy outcomes) generated after reboxetine was approved in Europe in the late 1990s has been analysed by these authorities. The reason for the difference in approval status of reboxetine between Europe and the US thus remains unclear.

Conclusions and policy implications

Our analysis of a comprehensive evidence base of published and unpublished trials of reboxetine compared with placebo or SSRIs in adults with major depressive disorder indicates that reboxetine is, overall, an ineffective and potentially harmful antidepressant. Published evidence on reboxetine has been substantially affected by publication bias, underlining the urgent need for mandatory publication of clinical trial data, including data on older agents.

What is already known on this topic

- Reboxetine has been approved for the treatment of major depression in many European countries, but the application for approval was rejected in the United States
- Doubts have been raised about the efficacy of reboxetine
- Research into antidepressants is particularly affected by publication bias

What this study adds

- Overall, reboxetine is not effective for the treatment of major depressive disorder
- We found a higher rate of patients affected by adverse events than with placebo and higher withdrawal rates owing to adverse events than with placebo and fluoxetine
- This meta-analysis provides a striking example of publication bias in which the previously favourable risk-benefit profile of reboxetine shown in published trials is reversed by the addition of unpublished data
- Post-approval regulatory decisions (for example, reimbursement decisions based on the findings of health technology assessment reports) might be affected by publication bias
- Our findings underline the need for mandatory publication of clinical trial results

Notes

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Footnotes

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- Contributors: DE coordinated and BW supervised the review. DE, ML, UG, MH, TK, MG, and BW designed the protocol. UG and MK planned and did the statistical analyses. DE, ML, and MG selected studies. MFK did the data extraction. All authors (except MFK)

assessed studies. DE wrote the first draft of the paper. All authors contributed to data interpretation and to critical revision of the paper, and have seen and approved the final version. BW is the guarantor.

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- Competing interests: All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any company for the submitted work; DE was employed by H Lundbeck A/S, Copenhagen, between January 2006 and April 2007; MH received remuneration from Boehringer Ingelheim and Lilly Pharma for three talks on depression guidelines in 2008; and UG, MK, TK, MFK, and BW are employees of IQWiG. DE is a former employee of IQWiG. In order to produce unbiased health technology assessment reports, the institute depends on access to all of the relevant data on the topic under investigation. The authors therefore support the mandatory worldwide establishment of trial registries and study results databases. ML and MH were involved in the development of the German Disease Management Guideline on Depression.
- Ethical approval: Not required.
- Data sharing: The full (German) version of the health technology assessment report (including the search strategy) and the clinical study reports on reboxetine are available on the IQWiG website (www.iqwig.de).

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Staff Report on GlaxoSmithKline and the Diabetes Drug Avandia [23.06 MB]
Senators' Letter to the FDA with Attachments [5.53 MB]

Grassley, Baucus Release Committee Report on Avandia

Senators Express Concern About FDA's Role in Protecting Patients in Ongoing Avandia Study

WASHINGTON – Senator Max Baucus, Chairman of the Committee on Finance, and Senator Chuck Grassley, Ranking Member, today released a committee report based on a twoyear inquiry of the diabetes drug Avandia. The senators also asked the Food and Drug Administration to describe what steps the agency has taken to protect patients in an ongoing Avandia clinical trial, and why the study is allowed to continue, given that the FDA itself estimated that the drug caused approximately 83,000 excess heart attacks between 1999 and 2007. In 2008, FDA officials called the clinical trial, as then-designed, "unethical and exploitative" of patients.

"There's a real problem when FDA's office that reviews drugs that are on the market is an unequal player in drug safety efforts," Grassley said. **"It doesn't make any sense to have these experts, who study drugs after they have been on the market for several years, under the thumb of the officials who approved the drug in the first place and have a natural interest in defending that decision. The Avandia case may be the most alarming example of the problem with this set-up. Both the FDA and Congress need to take every step possible to establish independence for post-market surveillance. The Institute of Medicine has made recommendations. It's a matter of sound science and public safety."**

"Americans have a right to know there are serious health risks associated with Avandia and GlaxoSmithKline had a responsibility to tell them. Patients trust drug companies with their health and their lives and GlaxoSmithKline abused that trust," Baucus said. **"We will continue watching closely and working with the FDA to make sure patients and doctors are aware of the risks associated with Avandia and all drugs so they can make safe and informed decisions when choosing their medicines."**

The committee report explores when the Avandia manufacturer, GlaxoSmithKline, became aware of heart attack risks associated with the drug, whether the company sufficiently warned patients and the FDA of the dangers, and steps the company apparently took to create doubt regarding negative findings about the drug. The report was developed over the last two years by committee investigators who reviewed more than 250,000 pages of documents provided by GlaxoSmithKline, the FDA, and several research institutes. Committee investigators also conducted numerous interviews and phone calls with GlaxoSmithKline, the FDA and anonymous whistleblowers. The report can be found at finance.senate.gov.

Baucus and Grassley directed the report over concerns that Avandia and other highprofile drugs such as Vioxx put public safety at risk because the FDA has been too cozy with drug makers and has been regularly outmaneuvered by companies that have a financial interest in downplaying or under-exploring potential safety risks. In 2007, Congress enacted legislation giving the FDA some new tools to better protect patients from harm caused by drugs that are brought to market without sufficient safety oversight or consumer warnings. However, the legislation did not fix a fundamental problem at the FDA -- the imbalance between the office responsible for monitoring the safety of

drugs after approval and the office that puts drugs on the market in the first place.

The FDA has overlooked or overridden safety concerns cited by its own officials, as appears to be the case with the ongoing Avandia study. The text of the Baucus-Grassley letter to the FDA on the Avandia study follows here.

February 18, 2010

The Honorable Margaret A. Hamburg, MD
Commissioner
U.S. Food and Drug Administration
White Oak Building 1
10903 New Hampshire Avenue
Silver Spring, MD 20993

Dear Commissioner Hamburg:

As senior members of the United States Senate and Chairman and Ranking Member of the Committee on Finance (Committee), we have a duty under the Constitution to conduct oversight into the actions of executive branch agencies, including the Food and Drug Administration (FDA). In this capacity, we must ensure that FDA properly fulfill their mission to advance the public's welfare, safeguard the nation's drug supply, and protect patients participating in clinical trials.

We recently released a report raising concerns about Avandia, a diabetes drug made by GlaxoSmithKline (GSK). We began this inquiry after the New England Journal of Medicine published a study in May 2007 warning of the possible cardiovascular risk of Avandia. Our report was based on a review of hundreds of thousands of pages of internal GSK documents and concluded:

The totality of evidence suggests that GSK was aware of the possible cardiac risks associated with Avandia years before such evidence became public.… Based on this knowledge, GSK had a duty to sufficiently warn patients and the FDA of its concerns in a timely manner. Instead, GSK executives intimidated independent physicians, focused on strategies to minimize findings that Avandia may increase cardiovascular risk, and sought ways to downplay findings that the rival drug ACTOS (pioglitazone) might reduce cardiovascular risk.

In 2007, the FDA asked GSK to perform a cardiovascular safety trial, called TIDE (Thiazolidinedione Intervention With Vitamin D Evaluation), to compare Avandia to other diabetes treatments such as ACTOS (piolglitazone). According to clinicaltrials.gov, the TIDE trial is currently recruiting patients. [ATTACHMENT A]

In response to several document requests made to the FDA, we received and reviewed an analysis conducted by two FDA safety officials. It is our understanding that this analysis, conducted in October 2008, reviewed all available studies comparing rosiglitazone (Avandia) to pioglitazone (ACTOS). The analysis by these FDA officials raise some alarms. For instance, they wrote:

[T]here is no evidence that rosiglitazone confers any unique health benefits over pioglitazone while there is strong evidence that rosiglitazone confers an increased risk of [heart attacks] and heart failure compared to pioglitazone. [ATTACHMENT B]

Even more alarming, they concluded that "any proposed head-to-head trial of rosiglitazone vs. pioglitazone would be unethical and exploitative."

Two days after releasing this analysis, one of these same safety officers reviewed the protocol for the TIDE trial. This safety officer wrote that because of cardiovascular concerns with Avandia "the safety of the study itself cannot be assured, and is not acceptable." [Attachment C]

After reading these documents, we would like to know what steps the FDA has taken to protect patients in the TIDE trial, and why this trial is allowed to continue. We would also like to know if the Office for Human Research Protection (OHRP) was notified about the safety concerns of the TIDE trial identified by the FDA. Further, we were alarmed to learn that the warnings from these safety officers do not appear to be addressed in the consent form that was handed out to patients that were enrolled in the study. [Attachment D]

We look forward to hearing from you by no later than March 4, 2010.

Sincerely,

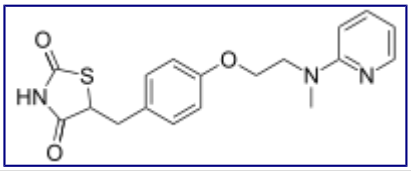
Max Baucus
Chairman

Chuck Grassley
Ranking Member

Rosiglitazone

From Wikipedia, the free encyclopedia

Rosiglitazone



Systematic (IUPAC) name
(*RS*)-5-[4-(2-[methyl(pyridin-2-yl)amino]ethoxy)benzyl]thiazolidine-2,4-dione
Clinical data
Trade names	Avandia
AHFS/Drugs.com	monograph
MedlinePlus	a699023
Licence data	EMA:Link, US FDA:link
Pregnancy cat.	B3 (AU) C (US)
Legal status	POM (UK) ℞-only (US)
Routes	Oral
Pharmacokinetic data
Bioavailability	99%
Protein binding	99.8%
Metabolism	Hepatic (CYP2C8-mediated)
Half-life	3-4 hours
Excretion	Renal (64%) and fecal (23%)
Identifiers
CAS number	122320-73-4 ✓
ATC code	A10BG02
PubChem	CID 77999
IUPHAR ligand	1056
DrugBank	DB00412
ChemSpider	70383 ✓
UNII	05V02F2KDG ✓
KEGG	D00596 ✗
ChEBI	CHEBI:50122 ✓
ChEMBL	CHEMBL121 ✗
Chemical data
Formula	$C_{18}H_{19}N_3O_3S$
Mol. mass	357.428 g/mol

SMILES[show]

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✗ **(what is this?) (verify)**

Rosiglitazone is an antidiabetic drug in the thiazolidinedione class of drugs. It works as an insulin sensitizer, by binding to the PPAR receptors in fat cells and making the cells more responsive to insulin. It is marketed by the pharmaceutical company GlaxoSmithKline (GSK) as a stand-alone drug (Avandia) and in combination with metformin (Avandamet) or with glimepiride (Avandaryl). Annual sales peaked at approximately $2.5bn in 2006, but declined after reports of adverse effects. The drug's patent expires in 2012.[1]

Some reports have found rosiglitazone is associated with an increased risk of heart attacks, but other reports have not found a statistically significant increase. Concern about adverse effects has reduced the use of rosiglitazone despite its sustained effects on glycemic control.[2] The drug is currently the subject of over 13,000 lawsuits against GSK.[3][*dead link*] As of July 2010, GSK has agreed to settlements on more than 11,500 of these suits.

The drug is controversial in the U.S. Some reviewers have concluded rosiglitazone caused more deaths than pioglitazone (Actos), and have recommended rosiglitazone be taken off the market, but an Food and Drug Administration panel disagreed, and it remains on the market in the U.S., subject to significant restrictions.[4] From November 18, 2011, the federal government will not allow Avandia to be sold without a prescription from certified doctors. Patients will be required to be informed of the risks associated with its use, and the drug will be required to be purchased by mail order through specified pharmacies.[5]

In Europe, the European Medicines Agency (EMA) recommended in September 2010 that the drug be suspended from the European market. However, patients currently taking rosiglitazone are advised to discuss alternative options during their next physician appointment.[6][7] In New Zealand, rosiglitazone was withdrawn from the market in April 2011.[8]

Pharmacology

Rosiglitazone is a member of the thiazolidinedione class of drugs. Thiazolidinediones act as insulin sensitizers. They reduce glucose, fatty acid, and insulin blood concentrations. They work by binding to the peroxisome proliferator-activated receptors (PPARs). PPARs are receptors on the membrane of the cell nucleus. Thiazolidinediones enter the cell, bind to the nuclear receptors, and affect the expression of DNA. The several PPARs include PPARα, PPARβ/δ, and PPARγ. Thiazolidinediones bind to PPARγ.

Avandia 2-mg oral tablet

PPARs are expressed in fat cells, cells of the liver, muscle, heart, and inner wall (endothelium) and smooth muscle of blood vessels. PPARγ is expressed mainly in fat tissue, where it regulates genes involved in fat cell (adipocyte) differentiation, fatty acid uptake and storage, and glucose uptake. It is also found in pancreatic beta cells, vascular endothelium, and macrophages.[9] Rosiglitazone is a selective ligand of PPARγ and has no PPARα-binding action. Other drugs bind to PPARα.

Rosiglitazone also appears to have an anti-inflammatory effect in addition to its effect on insulin resistance. Nuclear factor kappa-B (NF-κB), a signaling molecule, stimulates the inflammatory

pathways. NF-κB inhibitor (IκB) downregulates the inflammatory pathways. When patients take rosiglitazone, NF-κB levels fall and IκB levels increase.[10]

Rosiglitazone may also benefit patients with Alzheimer's disease who do not express the ApoE4 allele.[11] This is the subject of a clinical trial currently underway.[12]

Rosiglitazone may also treat mild to moderate ulcerative colitis, due to its anti-inflammatory properties as a PPAR ligand.[13]

A clinical trial has suggested these agents may be of use in treating malaria.[14]

Adverse effects

Heart disease

Some studies concluded rosiglitazone increases fatalities from heart disease, but other studies do not.

A study in 2007 has been widely cited as finding Avandia may increase the risk of heart attack by as much as 43%.[15][16]

A meta-analysis in May 2007 reported the use of rosiglitazone was associated with a significantly increased risk of heart attack (odds ratio = 1.43, 95% confidence interval, 1.03 to 1.98; P=0.03), and an even higher risk of death from all cardiovascular diseases (odds ratio = 1.64).[17] The U.S. Food and Drug Administration (FDA) issued an alert on May 21, 2007.[18] On July 30, 2007, an Advisory Committee of the Food and Drug Administration concluded the use of rosiglitazone for the treatment of type 2 diabetes was associated with a greater risk of myocardial ischemic events (including heart attacks) than a placebo, but data from several long term, prospective clinical trials showed when rosiglitazone was compared to metformin, or sulfonylurea, there was no difference in the risk of heart attack. These data, coupled with the meta-analysis, prompted the FDA to state the data on the association between rosiglitazone and myocardial ischemia were inconclusive. The meta-analysis was not supported by an interim analysis of the trial designed to evaluate this, and several other reports have failed to conclude the controversy. Graham argued rosiglitazone caused 500 more heart attacks and 300 more heart failures than its main competitor.

At the same time, a report by the Senate Finance Committee accused GlaxoSmithKline of knowing about the drug's risks well before they became public. The report also criticized the FDA for letting clinical trials continue, despite 83,000 heart attacks from 1999 to 2007 that the FDA linked to rosiglitazone. This Senate Committee report from November 2007 is entitled "The Intimidation of Dr. John Buse and the Diabetes Drug Avandia". The title refers to (temporarily successful) efforts made by GSK beginning in 1999 to intimidate an academic scientist from continuing to suggest Avandia had cardiovascular risk. The drug now bears a black box warning about exactly this risk. Further efforts by the vendors to protect their product are also described at Senate.gov, searchbox "Avandia". GlaxoSmithKline maintains the drug is safe and the Senate report did not consider scientific evidence or the company's efforts to make known its concerns to the parties involved. However, the FDA still recommends patients continue taking it unless their doctors tell them otherwise.[19][20]

The 2009 RECORD study, an open-label trial published in the *Lancet*, found no increase in cardiovascular hospitalisation or death with rosiglitazone compared to metformin plus sulfonylurea, but the rate of heart failure causing admission to a hospital or death was significantly increased.[21]

In February 2010, David Graham, the FDA's associate director of drug safety, recommended rosiglitazone be taken off the market. In June 2010, Graham *et al*., published a retrospective study

of 227,571 elderly American patients, comparing roziglitazone to pioglitazone, the other thiazolidinedione marketed in the United States. The authors concluded rosiglitazone was associated with "an increased risk of stroke, heart failure, and all-cause mortality and an increased risk of the composite of AMI, stroke, heart failure, or all-cause mortality in patients 65 years or older".[22] The number needed to harm with roziglitazone was sixty.

Both TZDs are contraindicated in patients with NYHA Class III and IV heart failure.

The controversy over adverse effects has dramatically reduced the use of rosiglitazone, despite its important and sustained effects on glycemic control.[2] No studies have shown that rosiglitazone reduces the risk of stroke, amputation, heart attack, blindness, neuropathy or renal failure.

A meta-analysis of observational studies released in March, 2011, provides more evidence that rosiglitazone is associated with a higher risk of heart failure, myocardial infarction and death than a similar agent, pioglitazone. The meta-analysis had 16 observational studies involving 810 000 patients taking rosiglitazone or pioglitazone.[23]

Stroke

Avandia has been linked to stroke. In a study led by FDA scientist David J. Graham, MD, MPH, by comparing the patient records of elderly patients using Avandia and alternative drug Actos, found Avandia increased the risk of stroke by over 27%.[24][25][26]

Bone fractures

GlaxoSmithKline reported a greater incidence of fractures of the upper arms, hands and feet in female diabetics given rosiglitazone compared with those given metformin or glyburide.[27] The information was based on data from the ADOPT trial.[28] The same increase has been found with pioglitazone (Actos), another TZD.

Eye damage

Both rosiglitazone and pioglitazone have been suspected of causing macular edema, which damages the retina of the eye and causes partial blindness. Blindness is also a possible effect of diabetes, which rosiglitazone is intended to treat. One report[29] documented several occurrences and recommended discontinuation at the first sign of vision problems.

Hepatotoxicity

Moderate to severe acute hepatitis has occurred in several adults who had been taking the drug at the recommended dose for two to four weeks. Plasma rosiglitazone concentrations may be significantly increased in patients with pre-existing hepatic impairment.[30]

Oral contraceptives

Rosiglitazone decreases the effectiveness of oral contraceptives.[*medical citation needed*]

Society and culture

Sales

US sales of the drug were of $2.2 billion in 2006.[31] Sales in 2Q 2007 down 22% compared to

2006.[32] 4Q 2007 sales down to $252 million.[33]

Though sales have gone down since 2007 due to safety concerns, Avandia sales for 2009 totalled $1.2 billion worldwide.[20]

Lawsuits

The Guardian reported lawsuits over the drug could total from $1 billion to $6 billion, based on research by analysts for UBS, who say 13,000 suits have been filed.[34] Included among those suing: Santa Clara County, California, which claims to have spent $2 million on rosiglitazone between 1999 and 2007 at its public hospital and is asking for "triple damages".[35] In May 2010, GlaxoSmithKline (GSK) reached settlement agreements for some of the cases against the company, agreeing to pay $60 million to resolve 700 suits.[36] In July 2010, GSK reached settlement agreements to close another 10,000 of the lawsuits against it, agreeing to pay about $460 million to settle these suits.[37][38] In a statement, Michael Miller, the attorney representing 1,500 patients in the suit, said about the settlement, "It's a compromise that allows both sides to put this behind them and move on."[39]

Government investigations

The drug has been under investigation in the US and in Europe. In September 2010, the U.S. Food and Drug Administration (FDA) decided rosiglitazone can remain available, but with certain restrictions. Also, the European Medicines Agency has decided to stop making all rosiglitazone-containing antidiabetes medication available in Europe.[40] The FDA has decided on revising its prescribing information and medication guides for all rosilitazone containing medicines. The US label for rosiglitazone (Avandia, GlaxoSmithKline) and all rosiglitazone-containing medications (Avandamet and Avandaryl) now include the additional safety information and restrictions.[41] The revised labels restrict use to patients already taking a rosiglitazone-containing medicine or to new patients who are unable to achieve adequate glycemic control on other diabetes medications and to those, who in consultation with their healthcare provider, have decided not to take Actos (pioglitazone) or other pioglitazone-containing medicines for medical reasons.[42]

United States investigations

The FDA began investigating the drug in 2007 after reports it likely caused an increased risk in heart attacks, but following a 2007 study, an FDA advisory panel agreed Avandia did not cause a statistically significant increase in heart attacks. The FDA voted to keep the drug on the market; a few months later, however, the agency added a black-box warning about potential heart risks of Avandia.[43] A study was conducted evaluating the geographic variation in the use of rosiglitazone following the black box warning issued in 2007. Residual use varied by state, which may be explained by uncertainty regarding how to translate FDA warnings into practice, by differences in coverage policies among health plans and in formularies among states, and by regional differences in the distribution and influence of pharmaceutical marketing, specialists, and opinion leaders.[44]

In 2007, a panel of independent researchers reported Avandia could, in fact, increase patients' risks of heart attack, but they recommended it remain on the market. An FDA oversight committee voted in 2007, eight to seven, to accept that advice and keep it on the market.[45]

GlaxoSmithKline is currently being investigated by the FDA and the US Congress regarding Avandia.

Senators Democrat Max Baucus and Republican Charles Grassley filed a report urging GSK to withdraw Avandia in 2008 due to the side effects. The report noted the drug caused 500 avoidable

heart attacks a month, and Glaxo officials sought to intimidate doctors who criticized the drug. It also said GSK continued to sell and promote the drug despite knowing the increased risk of heart attacks and stroke.[3]

The Senate Finance Committee, in a panel investigation, revealed emails from GSK company officials that suggest the company downplayed scientific findings about safety risks dating back to 2000. It was also alleged by the committee that the company initiated a "ghostwriting campaign", whereby GSK sought outside companies to write positive articles about Avandia to submit to medical journals.[46] GSK defended itself by presenting data that its own tests found Avandia to be safe, although an FDA staff report showed the conclusions were flawed.[47] Many studies have found the drug to have serious safety concerns.[48]

On July 14, 2010, after two days of extensive deliberations, the FDA panel investigating Avandia came to a mixed vote. Twelve members of the panel voted to take the drug off the market, 17 recommended to leave it on but with a more revised warning label, and three voted to keep it on the market with the current warning label.[49][50] The panel has come to some controversy, however; on July 20, 2010, one of the panelists was discovered to have been a paid speaker for GlaxoSmithKline, arrousing questions of a conflict of interest. This panel member was one of the three who voted to keep Avandia on the market with no additional warning labels.[51][52][53] The FDA is expected to vote soon on what to do next in regards to Avandia, though the FDA almost always agrees with its panel votes.

In 2012, the U.S. Justice Department announced GlaxoSmithKline had agreed to plead guilty and pay a $3 billion fine, in part for withholding the results of two studies of the cardiovascular safety of Avandia between 2001 and 2007.[54]

European investigations

According to a probe by the *British Medical Journal* in September 2010, the United Kingdom's Commission on Human Medicines recommended to the Medicines and Healthcare Products Regulatory Agency (MHRA) back in July 2010, to withdraw Avandia sale because its "risks outweigh its benefits". Additionally, the probe revealed that in 2000, members of the European panel in charge of reviewing Avandia prior to its approval had concerns about the long-term risks of the drug.[55][56] The European Medicines Agency recommended on 23 September 2010 that Avandia be suspended from the European market.[6][7]

New Zealand

Rosiglitazone was withdrawn from the New Zealand market April 2011 because Medsafe concluded the suspected cardiovascular risks of the medicine for patients with type 2 diabetes outweigh its benefits.[57]

Controversy and response

Following the reports in 2007 that Avandia can significantly increase the risk of heart attacks, the drug has been controversial. A 2010 article in *Time* uses the Avandia case as evidence of a broken FDA regulatory system that "may prove criminal as well as fatal". It details the disclosure failures, adding, "Congressional reports revealed that GSK sat on early evidence of the heart risks of its drug, and that the FDA knew of the dangers months before it informed the public." It reports, "the FDA is investigating whether GSK broke the law by failing to fully inform the agency of Avandia's heart risks", according to deputy FDA commissioner Dr. Joshua Sharfstein. GSK threatened academics who reported adverse research results, and received multiple warning letters from the FDA for deceptive marketing and failure to report clinical data.[58]

The maker of the drug, GlaxoSmithKline, has dealt with serious backlash against the company for the drug's controversy.[59] Sales on the drug dropped significantly after the story first broke in 2007, dropping from $2.5 billion in 2006 to less than $408 million in 2009 in the US.[60]

In response to the rise in risk of heart attacks, the Indian government ordered GSK to suspend its research study, called TIDE, in 2010.[61][62] Takeda Pharmaceuticals responded to the controversy by running a large advertising campaign for its rival diabetes drug Actos, first in 2007 and again in 2010.[63] The FDA also halted the TIDE study in the United States.[64][64]

Three doctors' groups, the Endocrine Society, the American Diabetes Association and the American Association of Clinical Endocrinologists, urged patients to continue to take the drug as it would be much worse to stop all treatment, despite any associated risk, but that patients could consult their doctors and begin a switch to a different drug if they or their doctors find concern.[65][66][67] The American Heart Association said in a statement in June 2010: " ...the reports deserves serious consideration, and patients with diabetes who are 65 years of age or older and being treated with rosiglitazone should discuss the findings with their prescribing physician....". "For patients with diabetes, the most serious consequences are heart disease and stroke, and the risk of suffering from them is significantly increased when diabetes is present. As in most situations, patients should not change or stop medications without consulting their healthcare provider."[68][69]

In Nov 2011, in a unique case, all sales of rosiglitazone were directed by the U.S. Department of Health and Human Services to go through Liberty Medical in Port St. Lucie, Florida. As a result of this action, the price of the drug immediately more than doubled, and in some cases, increased 250%.[*citation needed*]

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64.^ *a* *b* http://www.foodconsumer.org/newsite/Non-food/Drug/fda_orders_glaxo_to_stop_an_avandia_trial_2307100700.html
65.^ "Don't dump Avandia, diabetes groups urge patients". *Reuters*. 2010-07-15.
66.^ Maugh II, Thomas H. (2010-07-15). "Patients taking Avandia should keep on doing so, doctor groups say". *The Los Angeles Times*.
67.^ Katz, Neil (2010-07-16). "Avandia News: What You Need to Know". *CBS News*.
68.^ "Booster Shots". *The Los Angeles Times*. 2010-06-29.
69.^ http://www.redorbit.com/news/health/1892007/american_heart_association_comment_advisory_committee_recommends_that_us_food/index.html?source=r_health

External links

- Rosiglitazone bound to proteins in the PDB: S-rosiglitazone, R-rosiglitazone
- Official website
- MedlinePlus article
- Medscape
- ClinicalTrials.gov *NCT00265148 Brain Imaging Study of Rosiglitazone Efficacy and Safety in Alzheimer's Disease*
- U.S. National Library of Medicine: Drug Information Portal - Rosiglitazone

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This page was last modified on 24 August 2012 at 17:28.

February 22, 2010 2:36 PM

Meet Glaxo's Fixer -- The Man Who Scuttles Drug Critics With One Phone Call

By **Jim Edwards**

It's worth a look inside the Senate Finance Committee's 342-page report on **GlaxoSmithKline** (GSK)'s **Avandia** diabetes medicine if only for the allegations of cloak-and-dagger intimidation the company aimed at scientists who had bad things to report about the drug. In there you will meet Dr. **Tachi Yamada** (pictured), GSK's fixer on Avandia, who with just a few phone calls to your superiors can derail your drug research.

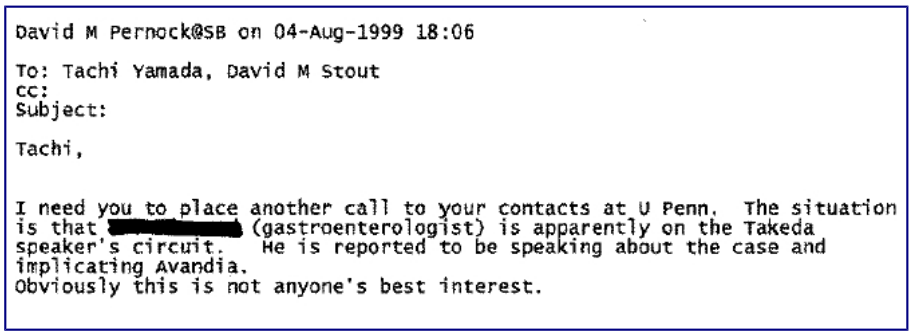
Download the report here.

FDA reviewers believe Avandia caused 500 extra heart attacks per month, and Senators **Charles Grassley** and **Max Baucus** are asking the agency to remove the drug from the market. GSK has mounted a feisty defense, saying that the Senate report "cherry picks" information and that "the scientific evidence simply does not establish that Avandia increases cardiovascular ischemic risk or causes myocardial ischemic events." Seven trials have not shown a statistical link between Avandia and heart attacks, GSK insists.

GSK's combative stance is paralleled in the report. That document suggests that if you were an independent scientist doing a study of Avandia's side effects, then Yamada, GSK's top R&D man, would make some calls and your study would either be spiked, leaked pre-publication, or rubbished in the press by GSK's pr machine. Said one **University of Pennsylvania** scientist, whose case study of a single patient with liver failure ended up not being published:

> I have never encountered anything like this in my career. I don't even know how [GSK] knew that we were publishing. It's the kind of thing you imagine happening on TV.

Here's a sample from Yamada's email, in which former GSK president **David Stout** asks Yamada to "place another call to your contacts" about some research that is "not [in] anyone's best interest":



David M Pernock@SB on 04-Aug-1999 18:06

To: Tachi Yamada, David M Stout
CC:
Subject:

Tachi,

I need you to place another call to your contacts at U Penn. The situation is that [redacted] (gastroenterologist) is apparently on the Takeda speaker's circuit. He is reported to be speaking about the case and implicating Avandia.
Obviously this is not anyone's best interest.

The report gives the best details regarding Dr. **John Buse**, a professor of medicine at the **University of North Carolina**. Buse appeared at conferences and had written to the FDA to say that he suspected heart problems in Avandia in 1999:

> According to GSK emails made available to the Committee, GSK executives labeled Dr. Buse a "renegade" and silenced his concerns about Avandia by complaining to his superiors at UNC and threatening a lawsuit. The call to Dr. Buse's superiors was made by Dr. Tachi Yamada, then GSK's head of research.

Yamada denied he was making calls to intimidate Buse:

> Instead, Dr. Yamada argued that he had made the call to determine if Dr. Buse was making legitimate statements or if he was possibly on the payroll of a GSK rival.

Another UPenn physician said the calls had a chilling effect:

> "It was really ridiculous. It was a case report and I had no intention of bringing down GSK. I just wanted people to know." The physician added, "It left a really bad taste in my mouth. After that happened, I said that I would never work for a drug company."

The report also gives more background detail on the famous battle GSK had with Dr. **Steven Nissen** of the Cleveland Clinic. It was Nissen's analysis of Avandia data that first raised public concerns about Avandia and heart attacks. The report says the study was leaked to GSK ahead of publication, and that:

> ... allowed GSK to launch a public relations plan to protect Avandia.

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