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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES
E. S. D.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



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Ref.	
EXPEDIENTE	05 117551A
PATENTE	DERIVADOS DE CARBOSTIRILO Y ESTABILIZANTES DEL ESTADO DE ANIMO PARA TRATAR TRASTORNOS DEL MISMO.
CLASE	A61K31/19; A61K31/47; A61K31/497, A61P25/24
SOLICITANTE	OTSUKA PHARMACEUTICAL CO., LTD.
TRAMITE	PATENTE
EVENTO	REGISTRO
ACTUACION	RECURSO DE REPOSICIÓN RESOLUCIÓN No. 79480 DE DICIEMBRE 30 DE 2011

El suscrito GERMAN A. CUBILLOS MENDOZA, abogado en ejercicio, con C.C. N° 19'397.479 de Bogotá y T.P. N° 38.422 del C. S. de la J. actuando en mi calidad de apoderado de la sociedad OTSUKA PHARMACEUTICAL CO., LTD., sociedad domiciliada en Tokio, Japón, por el presente y dentro del término legal interpongo el recurso de reposición contra la Resolución de la referencia, por medio de la cual se niega la patente de invención del rubro, a fin de que se revoque y en su lugar se conceda el privilegio de la patente de invención, de conformidad con los siguientes argumentos y alegatos:

1. Aripiprazol como un antipsicótico atípico

Como se explica más detalladamente a continuación, el aripiprazol pertenece a una nueva generación de antipsicóticos atípicos y cuenta con un perfil farmacológico totalmente distinto al de los antipsicóticos atípicos conocidos anteriormente.

Por lo tanto, el experto en la materia no esperaría que los antipsicóticos atípicos utilizados en el estado de la técnica podrían ser reemplazados por el aripiprazol. Sobre esta cuestión se hace referencia en los Anexos 1-3. Estos documentos se publican después de la fecha de prioridad de la presente solicitud, aunque como artículos de reseña, ambos confirman las propiedades farmacológicas de los antipsicóticos atípicos, y reflejan el conocimiento que sobre la materia tienen los expertos.

- 1.1. El Anexo 1 (Iqbal, Rinsho Seishin Yakuri (Japanese Journal of Clinical Psychopharmacology) , Volúmen. 9, No. 12, páginas 2503-2511 (2006)), Revista Japonesa de Psicopatología Clínica, es un artículo de reseña sobre el aripiprazol. También se adjunta la traducción al inglés de los capítulos II y III.

La olanzapina, clozapina, risperidona, ziprasidona y quetiapina pertenecen a la segunda generación de antipsicóticos atípicos (ver capítulo II), mientras que el aripiprazol es el primero de la tercera generación de antipsicóticos atípicos (ver capítulo III).

Tal como se muestra en la tabla 1, el perfil de los efectos farmacológicos del aripiprazol es totalmente distinto a los perfiles de la quetiapina, clozapina, risperidona, ziprasidona y olanzapina, empleados en D2, tal como se observa a partir de las diferencias de afinidad de unión a receptores (particularmente con respecto al receptor 5-HT_{1A}).

- 1.2. En el Anexo 2 (Farah, A., "Primary Care Companion J Clin. Psychiatry 7" (6), páginas 268-269 (2005)), la sección "*Definition of Atypicality*" explica que las categorías de típico o atípico se basaban originalmente en el grado de riesgo de síntomas extrapiramidales. Todos los antipsicóticos que se presentaron luego de la clozapina se clasificaron como atípicos, aunque son distintos unos de otros en cuanto al mecanismo de acción o afinidad de unión al receptor (ver último párrafo de la sección "*Definition of Atypicality*"): "A diferencia de medicamentos como los antipsicóticos convencionales o inhibidores de recaptación de serotonina, los antipsicóticos clasificados como atípicos no comparten, ni en un sentido amplio, el mismo perfil farmacológico general de otros miembros de su clase". Además, el capítulo "Aripiprazole" en la página 272, explica que el aripiprazol se diferencia de otros antipsicóticos atípicos como olanzapina, clozapina, risperidona, ziprasidona o quetiapina en cuanto a su afinidad a varios receptores y particularmente al receptor 5-HT_{1A}.

- 1.3 El Anexo 3 (A. Newman-Tancredi et al., Current Opinion in investigational Drugs, Volúmen 8, No. 7, páginas 539-554 (2007)) en la página 541, columna izquierda, líneas 12-20, muestra que la diferencia existente entre los antipsicóticos de tercera y segunda generación está en que los antipsicóticos de tercera generación tienen propiedades agonistas parciales de receptor tipo D₂ y propiedades agonistas (parciales) 5-HT_{1A}. En la página 542, columna izquierda, líneas 9-11, se indica que el aripiprazol es el primer y único agente antipsicótico que tiene un agonismo parcial con receptores tipo D₂.

Tal como se menciona anteriormente, el aripiprazol se diferencia de otros antipsicóticos no solo en las propiedades agonistas (parciales) 5-HT_{1A}, sino también en propiedades agonistas parciales de los receptores tipo D₂.

En resumen, los Anexos 1-3 brindan evidencia de que el aripiprazol tiene un perfil farmacológico y afinidades de unión al receptor diferentes al perfil farmacológico y a las afinidades de unión de la olanzapina, clozapina, risperidona, ziprasidona o quetiapina, por lo cual el experto en la materia no esperaría que el aripiprazol fuera intercambiable con otras drogas antipsicóticas atípicas.

2. La presente solicitud de patente posee Nivel Inventivo.

- 2.1. Considerando la Prueba Comparativa (Anexo 3) entregada el día 16 de Noviembre de 2010 en respuesta al Oficio No. 9533 del 30 de Julio de 2010, el problema que necesita solución a partir del estado más reciente de la técnica, se relaciona con la provisión de combinaciones de drogas más efectivas para el tratamiento de trastornos del estado del ánimo.
- 2.2. A partir de las combinaciones de técnicas anteriormente difundidas en D2 y D3, el experto en la materia no esperaría que los antipsicóticos atípicos como la olanzapina puedan reemplazarse con aripiprazol, ya que los perfiles y propiedades farmacológicas son totalmente distintas y no es posible hallar efectos comunes, que podrían generar expectativas respecto a la posibilidad de que las drogas pudieran ser intercambiables (ver numeral 2 de este escrito).
- 2.3. Además, los informes experimentales muestran que los sorprendentes avances surgen de forma sinérgica a partir de la combinación específica de aripiprazol con el estabilizante del estado de ánimo y que no se esperaba dicho avance considerando el efecto del aripiprazol tomado aisladamente. Tampoco se

esperaba dicho avance considerando el efecto producido por combinaciones que están dentro del estado de la técnica.

- 2.4. En vista de esta situación, para el experto en la materia no resulta obvio ni se deriva de manera evidente a partir del documento D2 ó D3, que el uso del aripiprazol en combinación con un estabilizante del estado de ánimo pueda brindar una combinación de drogas para el tratamiento de trastornos del estado del ánimo, que sea más efectiva que las combinaciones de drogas descritas según el estado de la técnica. En consecuencia, el tema en cuestión de la presente solicitud implica un nivel inventivo.
3. La Resolución de la referencia no se encuentra suficientemente motivada para destruir el nivel inventivo de la presente solicitud de patente.
 - 3.1 En D3 sin duda alguna se describe que el aripiprazol tiene actividad agonista parcial sobre los receptores 5-HT_{1A}. Sin embargo, dicha bibliografía no incluye tales descripciones ni sugerencias, como señaló el examinador en el primer párrafo de la página 8 de la Resolución No. 79480, donde decía que el aripiprazol es un antipsicótico atípico con propiedades similares a la olanzapina, clozapina, risperidona, quetiapina y demás.
 - 3.2 Por el contrario, como ya se dijo en este escrito, el aripiprazol hace parte de una nueva generación de antipsicóticos atípicos que tienen un perfil farmacológico completamente distinto al de los antipsicóticos conocidos, entre ellos la olanzapina, clozapina, risperidona, quetiapina, etc.
 - 3.3. El aripiprazol no tiene propiedades similares comunes a los antipsicóticos atípicos convencionales. A este respecto, todo lo incluido en D3 no es más que el simple descubrimiento de que el aripiprazol tiene actividad agonista parcial sobre los receptores 5-HT_{1A}.
 - 3.4. Entretanto, como dio a entender el examinador en referencia a la divulgación en D3, como el aripiprazol tiene actividad agonista parcial sobre los receptores 5-HT_{1A}, el aripiprazol es más eficaz en el tratamiento de la esquizofrenia y demás trastornos.
 - 3.5. D2, en cambio, describe claramente las diferencias entre los trastornos bipolares y la esquizofrenia (*"Trastorno bipolar es un ... trastorno psicológico claramente diferenciado de los trastornos psicóticos como la esquizofrenia"*: (Ver página 1, renglón 36 a la página 2, renglón 2).
 - 3.6. Además, ni D2 ni D3 enseñan o sugieren que la mejora en la eficacia del tratamiento de la esquizofrenia en todos los casos implique una mejora en la eficacia del tratamiento de los trastornos bipolares.

- 3.7. En ese sentido, aunque D2 describe los antipsicóticos atípicos como uno de los componentes de una composición, no hay razones para que una persona versada en la materia sustituya los antipsicóticos atípicos mencionados por justificada.
- 3.8. Evaluación precisa de los efectos logrados por la presente invención

Consideramos que la evaluación que hace la Resolución en mención, de los efectos logrados por la presente invención, es un sinsentido.

En otras palabras, la importancia de los efectos logrados por la presente invención radica no sólo en que la combinación actual de por sí muestra una mayor eficacia que las otras combinaciones en los trastornos bipolares, sino que un estabilizador del ánimo (como el topiramato), el cual no muestra mejora alguna en la eficacia de otros agentes cuando se combina con dicho agente, excepto cuando se combina con aripiprazol, caso en el cual la eficacia obtenida sólo con la administración del aripiprazol mejoró significativamente de modo sinérgico.

En otras palabras, el estabilizador del estado de ánimo puede ayudar a mejorar la eficacia del aripiprazol, caso diferente a los demás antipsicóticos atípicos.

- 3.9. Siendo más específicos, reafirmamos la siguiente Tabla 1, presentada el día 16 de Noviembre de 2010 dentro del anexo No. 3 y como respuesta al Oficio No. 9533 del 30 de Julio de 2010.

Como se puede ver, el topiramato muestra actividad sinérgica solamente cuando se combina con aripiprazol. Basta comparar las cifras en letra cursiva tipo Arial, (casillas tres, cuatro, cinco y seis) y sus correspondientes cifras en letra tipo Courier New (casillas siete, ocho, nueve y diez) de la Tabla 1.

Tabla 1. Efectos del tratamiento combinado de cada antipsicótico con topiramato sobre hiperlocomoción inducida por metanfetaminas en ratones

Tratamiento	Dosis (mg/kg)	N	Conteo Locomotor durante 60 min (significa $\pm$ S.E.M)
Vehículo 1 + Vehículo 2 + Vehículo 2	0 + 0 + 0	6	837.7 $\pm$ 99.7
Vehículo 1 + Vehículo 2 + Metanfetamina	0 + 0 + 3	6	15941.5 $\pm$ 1125.6 \$\$\$
Aripiprazol + Vehículo 2 + Metanfetamina	0.1 + 0 + 3	6	15727.7 $\pm$ 1141.4
Olanzapina + Vehículo 2 + Metanfetamina	0.2 + 0 + 3	6	13049.2 $\pm$ 1119.6
Clozapina + Vehículo 2 + Metanfetamina	3 + 0 + 3	6	11686.8 $\pm$ 1862.7
Risperidona + Vehículo 2 + Metanfetamina	0.01 + 0 + 3	6	13844.7 $\pm$ 1403.8
Aripiprazol + Topiramato + Metanfetamina	0.1 + 20 + 3	6	8270.0 $\pm$ 2076.4 **, ##
Olanzapina + Topiramato + Metanfetamina	0.2 + 20 + 3	6	13805.8 $\pm$ 1289.4
Clozapina + Topiramato + Metanfetamina	3 + 20 + 3	6	14372.2 $\pm$ 784.3
Risperidona + Topiramato + Metanfetamina	0.01 + 20 + 3	6	15199.3 $\pm$ 1071.6

Por lo tanto, consideramos que los efectos logrados por la presente invención son tan notables que no se podían prever en la divulgación en D2 o D3.

3.10. Conclusión sobre el elemento inventivo

Como ya se afirmó, consideramos que la presente invención tiene nivel inventivo con respecto a las divulgadas en D2 y D3, de manera individual o en conjunto.

- 3.11. En el ejemplo 4, como aparece en la especificación original, se describe que a los pacientes (diagnosticados con trastorno bipolar (I o II), manía aguda, o depresión bipolar) que tienen una puntuación en la Escala de Young para la evaluación de la Manía (YMRS)(Young Mania Rating Scale) por encima de 24 (página 66 de la Descripción (igual a folio 72) líneas 18 a 23, se les administró aripiprazol o metabolito de aripiprazol y uno o más de los estabilizadores del estado de ánimo, y como resultado, según lo indican las mediciones de parámetros como el YMRS y demás mediciones, se observó una normalización del estado de ánimo.

Transcribimos a continuación el texto referido en página 66 de la Descripción:

trastorno bipolar (I o II), manía aguda o depresión bipolar.

Los pacientes que varían en edad de 18 a 65 años en quienes se

diagnosticó con trastorno bipolar (I o II), manía aguda o

depresión bipolar, fueron evaluados para asegurar que

presentan una escala de calificación de manía Young de línea

de base (YMRS) con una calificación mayor de 24. Únicamente

- 3.12. Entretanto, a este respecto ha sido establecido, el método de medición y evaluación en la YMRS; es evidente para una persona versada en la materia que la normalización del estado de ánimo corresponde a la disminución en la YMRS.

Por tanto, las descripciones mencionadas anteriormente en el presente ejemplo 4 describen con suficiencia que las alternativas pretendidas para la carbamazepina, lamotrigina, gabapentina y la sal derivada de las mismas, enumeradas en la presente reivindicación 1, tienen el mismo efecto combinatorio que la combinación de aripiprazol con topiramato que representó el experimento ya enviado.

Conforme lo argumentado arriba, consideramos que debe otorgarse patente para la presente invención descrita en las reivindicaciones propuestas, por lo que solicitamos con el debido respeto, otorgar el privilegio de patente a la presente invención.

4. Por otra parte, notamos que la resolución de la referencia no se pronunció sobre la argumentación y los anexos que presentamos en nuestro memorial de respuesta fechado el 4 de noviembre de 2011.

El artículo 59 del Código Contencioso Administrativo, modificado por el art. 6, Decreto Nacional 2304 de 1989, prevé que:

“Concluido el término para practicar pruebas, y sin necesidad de auto que así lo declare, deberá proferirse la decisión definitiva. Esta se motivará en sus aspectos de hecho y de derecho, y en los de conveniencia si es del caso. La decisión resolverá todas las cuestiones que hayan sido planteadas y las que aparezcan con motivo del recurso, aunque no lo hayan sido antes.”

Lo que quiere decir es que a propósito de la presentación de los anexos 1, 2, y 3 en el escrito de fecha 4 de noviembre de 2011, que no fueron considerados por la administración, lo que impone la norma es una obligación a la Superintendencia de Industria y Comercio, División de Nuevas Creaciones, de decidir sobre todas las cuestiones planteadas por el peticionario en vía gubernativa, incluidas aquéllas que no hayan sido propuestas por él en instancias anteriores al acto definitivo, que es objeto de la reclamación.

En relación con lo anterior, el Honorable Consejo de Estado, en reiteradas ocasiones, ha expresado que, dentro las actuaciones administrativas, el funcionario competente debe hacer observancia de todas las pruebas presentadas antes de proferirse la decisión, cuando estas complementan las previamente aportadas dentro del término establecido en una norma.

5. La carga de la prueba en relación con la afirmación de que una solicitud de patente de invención adolece de nivel inventivo, pertenece al Examinador.

Artículo 18 de la Decisión 486

“Se considerará que una invención tiene nivel inventivo, si para una persona del oficio normalmente versada en la materia técnica correspondiente, esa invención no hubiese resultado obvia ni se hubiese derivado de manera evidente del estado de la técnica.”

El Tribunal de Justicia de la Comunidad Andina, en el proceso 36-IP-2010 interpreta entre otros el artículo 18 de la Decisión 486.

Apartes de la interpretación se transcriben a continuación:

“

(. . .) En este orden de ideas, se puede concluir que una invención goza de nivel inventivo cuando a los ojos de un experto medio en el asunto de que se trate, se necesita algo más que la simple aplicación de los conocimientos técnicos en la

materia para llegar a ella, es decir, que de conformidad con el estado de la técnica el invento no sea consecuencia clara y directa de dicho estado, sino que signifique un avance o salto cualitativo en la elaboración de la regla técnica.

El Manual para el Examen de Solicitudes de Patentes de Invención en las Oficinas de Propiedad Industrial de los Países de la Comunidad Andina, determina ciertos criterios para determinar el nivel inventivo que es importante transcribir:

“Se considera el nivel inventivo como un proceso creativo cuyos resultados no se deducen del estado de la técnica en forma evidente para un técnico con conocimientos medios en la materia, en la fecha de presentación de la solicitud o de la prioridad reconocida.

La cuestión para el examinador es si la invención reivindicada es o no evidente para un técnico en la materia. La existencia o la falta de cualquier ventaja técnica no es un criterio absoluto para reconocer o no un nivel inventivo. El examinador no debe determinar qué "cantidad" de nivel inventivo existe. El nivel inventivo existe o no, no hay respuestas intermedias.

El examinador no debe basarse en apreciaciones personales; toda objeción respecto a la falta de nivel inventivo de una invención debe probarse a partir del estado de la técnica.

Para juzgar si la invención definida por las reivindicaciones realmente se deriva de manera evidente del estado de la técnica, hay que determinar si carece de nivel inventivo cuando se consideran las diferencias entre ésta y el estado de la técnica más cercano. El examinador tiene la carga de probar que la invención carece de nivel inventivo y no sólo limitarse a establecer las diferencias entre la solicitud y dicho estado de la técnica.

Cuando se ha establecido la falta de novedad de la invención, no es necesario evaluar el nivel inventivo, dado que no existen diferencias entre la invención y el estado de la técnica.

Normalmente el estado de la técnica más cercano se encuentra en el mismo campo de la invención o trata de solucionar el mismo problema o uno semejante. Por ejemplo, en el área química el estado de la técnica más cercano puede ser aquél que describa un producto estructuralmente semejante al producto de la invención o un uso o actividad semejante al de la invención.

10.2 Método para la evaluación del nivel inventivo

10.2.1 Análisis problema-solución

Para determinar si el objeto de la reivindicación resulta obvio o se deriva de manera evidente del estado de la técnica se recurre, siempre que sea posible, al método problema-solución.

Para ello deben cumplirse las siguientes etapas:

- identificación del estado de la técnica más cercano;*
- identificación de las características técnicas de la invención que son diferentes con respecto a la anterioridad; y*
- definición del problema técnico a solucionar sobre la base del estado de la técnica más cercano.*

La pregunta es ¿qué problema resuelven las diferencias técnicas entre la invención y el estado de la técnica más cercano?

Dichas diferencias, en términos de características técnicas, entre la invención y el estado de la técnica más cercano representan la solución al problema técnico en cuestión.

Se debe definir el problema sin incluir elementos de la solución, porque entonces la solución sería evidente.

El problema técnico no siempre será el indicado en la solicitud y a veces tiene que ser replanteado en función de los resultados de la búsqueda. El estado de la técnica más cercano puede ser diferente del conocido por el solicitante y del cual él partió.

Evaluar, partiendo del estado de la técnica más cercano Y del problema técnico, si la invención reivindicada resulta obvia para la persona versada en la materia.

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

Una información técnica tiene siempre que ser considerada en su contexto, no debe extraerse ni interpretarse fuera de éste. Es decir, que la característica técnica que se está analizando debe buscarse en el mismo campo técnico o en uno que la persona versada en el oficio consideraría de todos modos.

Se debe tener en cuenta que la búsqueda de anterioridades se efectúa a posteriori, tomando como punto de partida la misma invención. Por lo tanto el examinador debe realizar el esfuerzo intelectual de colocarse en la situación que ha tenido que afrontar el técnico con conocimientos medios en la materia en un momento en que la invención no era conocida, es decir antes de la invención.

La invención reivindicada tiene que considerarse en su conjunto. Si consiste en una combinación de elementos no es válido argumentar que cada uno por separado es obvio, pues la invención puede estar en la relación (carácter técnico) entre ellos. La excepción a esta regla es el caso de yuxtaposición en el que los elementos se combinan sin que haya relación técnica entre las distintas características.

Una composición novedosa de AB donde A y B son conocidos de manera independiente, será inventiva si existe un efecto inesperado. Si el efecto se reduce a la suma de los efectos de A y B, no habrá nivel inventivo.

En resumen, el examinador debe plantearse las siguientes preguntas:

- *¿estaba un técnico con conocimientos medios en la materia en condiciones de plantearse el problema?;*
- *¿de resolverlo en la forma en que se reivindica: y*
- *¿de prever el resultado?*

Si la respuesta es afirmativa en los tres casos, no hay nivel inventivo.

(...)⁵.

El Juez Consultante deberá determinar si los documentos EP 0823846 y US 5.830.203,00 citados como anterioridades por la Superintendencia de Industria y Comercio, afectan el requisito de nivel inventivo en relación con la solicitud de patente, de conformidad con expresado en la presente providencia.(. . .) “

De conformidad también con la interpretación prejudicial arriba citada consideramos que la Resolución No. 79480 de la referencia, no demostró en forma satisfactoria la falta de nivel inventivo de la presente solicitud de patente.

ANEXOS

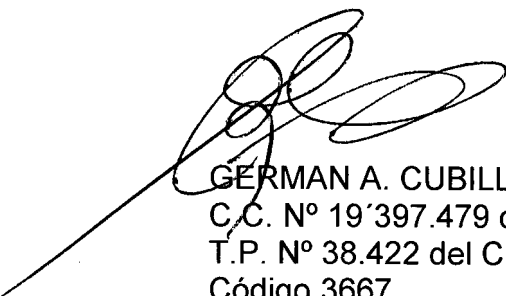
1. ANEXO 1 (Iqbal, Rinsho Seishin Yakuri (Japanese Journal of Clinical Psychopharmacology).
2. ANEXO 2 (Farah, A., "Primary Care Companion J Clin. Psychiatry 7").
3. ANEXO 3 (A. Newman-Tancredi et al., Current Opinion in investigational Drugs).

De esta manera dejo interpuesto el recurso de reposición con el propósito de que se revoque la Resolución recurrida No. 79480 de Diciembre 30 de 2011, y en su lugar se conceda el privilegio de patente de la referencia.

Nombre y dirección del recurrente
 Germán A. Cubillos Mendoza
 Calle 17 No. 8-49. Of. 408 de Bogotá

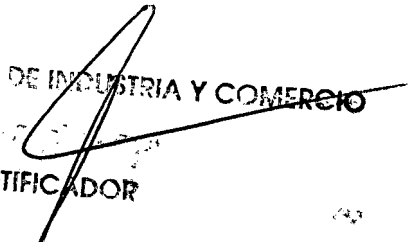
Sin otro particular me suscribo del Señor Ministro.

Cordialmente,


 GERMAN A. CUBILLOS MENDOZA
 C.C. N° 19.397.479 de Bogotá
 T.P. N° 38.422 del C.S. de la J.
 Código 3667

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
 Santafé de Bogotá, 31 ENE. 2012
 Presentando personalmente por Germán
A. Cubillos Mendoza
 C.C. 19.397.479 de Bogotá
 T.P. 38.422 del C.S. de la J.

Notificador Secretaria General


 SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
 NOTIFICADOR

ANEXO 1

米国での aripiprazole の臨床経験から

Naveed Iqbal*

監 訳

伊 豫 雅 臣**

伊豫 Aripiprazole も日本でいよいよ発売される時期（本座談会は2006年1月30日に実施）が迫ってまいりました。今回は、Iqbal 先生に、aripiprazole の適切な使い方についてお教えいただきます。

Iqbal 先生は、アメリカにおいて aripiprazole を1000例以上ご処方され、豊富なご経験を有しておられるとお聞きし、今回の講演を楽しみにしています。

本日は特に臨床的な視点から aripiprazole の処方実施例もいくつかご紹介いただけると聞いています。それではよろしくお願いいたします。

より適宜増減するが、1日量は30mgを超えないこと」としています。このため、米国の aripiprazole の効果・効果/用法・用量とはいくらか異なっていることをご了承の上、Iqbal 先生の講演をご覧ください。

はじめに

今日は、どうありがとうございます。まず、欧米で実施されました aripiprazole の開発経験をいくつか手短かにご紹介し、その後には治療以外で、私が経験した実施例について紹介します。なぜなら、アメリカにおいても aripiprazole 上市後、治療とは異なるいろいろなことを経験し学んできたことを伝えたいからです。

1. Aripiprazole 作用機序について

世界で最初のドパミン・システムスタビライザーです。aripiprazole の作用機序についてお話しします。皆さんよくご存知のノーベル生理学・医学賞を受賞された Arvid Carlsson 博士は、「確かにドパミン・アンタゴニストはいくつかの病気を治療しますが、多くの副作用が発現するため、ドパミン・アンタゴニストだけで治療を行うことは不十分であるため、ドパミン安定剤 (Dopaminergic Stabilizer) が必要である」と言われてきました。

このような背景の中、菊地哲朗氏をはじめとす

2006年9月10日追記 Aripiprazole (商品名: エビリファイ) は2006年6月8日に本邦でも発売された。本邦での aripiprazole の効果・効果は、統合失調症であり、その用法・用量は、「通常、成人には aripiprazole として1日6~12mgを開始用量。1日6~24mgを維持用量とし、1回又は2回に分けて経口投与する。なお、年齢、症状に

2006年1月30日、東京、八重洲富士閣ホテルにて録音。
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る大塚製薬の研究者の方々が aripiprazole を見出し、非常な努力のもと臨床試験を行って来られました。Aripiprazole で言われているドパミン・システムスタビライザーという概念は、統合失調症をはじめとする多くの精神疾患に意義あるものと言えると思います。

ドパミン神経経路は主に4つあり、そのうち2つは中脳辺縁系および中脳皮質系と呼ばれ、中脳辺縁系ではドパミン過剰により幻覚や妄想などを引き起こしますし、中脳皮質系ではドパミン低下により陰性症状や認知障害などを引き起こします。これは Carlsson 博士が指摘していますが、haloperidol は中脳辺縁系のドパミンを減少させるだけでなく、統合失調症ですでにドパミンが低下している中脳皮質系のドパミンをさらに減少させてしまいます。つまり、haloperidol は幻覚や妄想をコントロールしますが、中脳皮質系や前頭前野のドパミンをさらに低下させ、陰性症状を悪化させ、認知障害も起こすと考えられます。

ドパミン・システムスタビライザーやドパミン・パースシャルアゴニストのコンセプトはすでにお聞きおぼろしいと思いますが、aripiprazole は世界で最初のドパミン・システムスタビライザーです(図1)。Aripiprazole は、中脳辺縁系で過剰なドパミンにより陰性症状や幻覚、妄想が生じた場合、そのドパミンを遮断し、幻覚や妄想をコントロールしますが、前頭前野などで、ドパミンが低下している領域では活性化し、陰性症状や認知障害を改善します。

Aripiprazole は5-HT_{1A} 受容体パースシャルアゴニスト作用も有しており、抗不安薬としてお馴染みの buspirone (日本では未発売) のような、抗不安作用もあわせ持っています。まだ十分に実証されてはいませんが、5-HT_{1A} 受容体アゴニスト作用は前頭前野のドパミンもコントロールし、前頭皮質のドパミンを増加させ、認知機能も改善すると言われています。

II. 第二世代薬について

有効性と有用性について
これらの薬剤(図2)は、clozapine から始ま

- ・ドパミンD₂受容体パースシャルアゴニスト
 - D₂(D₁) 神経伝達を過剰に亢進した状態ではアゴニストとして作用する(陰性症状の改善)
 - D₂(D₁) 神経伝達を過剰に低下した状態ではアゴニストとして作用する(EPSの出現を軽減)
- ・α1アドレナリン受容体パースシャルアゴニスト
- ・α2アドレナリン受容体アンタゴニスト

図1 Aripiprazole の薬理特性

る第二世代薬です。第二世代薬の多くは、陽性症状や陰性症状の治療には有効ですが、非常に問題になる副作用があります。たとえば clozapine ですが、今でも日本で承認されていないのは、副作用が原因です。抗精神病薬の作用について議論すると、たいていはその「有効性」になります。製薬会社が我々に提示する試験成績も「有効性」に関するものがほとんどで「有用性」に関するものではありません。「有用性」とは、「有効性」だけではなく、「安全性・忍容性」も含まれ、患者にとって最も望ましい治療を指していると思います。つまり、ある患者にとって非常に優れた治療法があっても、副作用が多すぎると、患者は服薬を中止しますし、それにより「有用性」もなくなるからです。

さて、第二世代薬は「有用性」が低下していますが、これは明らかに副作用が原因です。Clozapine もそうですが、他の薬剤でも体重増加やメタボリック・シンドロームのような種々の副作用が生じています。メタボリック・シンドロームでは心毒性に対するリスクや心疾患の罹患率、死亡率が4~10倍上昇します。また、これまで clozapine や olanzapine により糖尿病に発症する糖尿病性ケトアシドーシスで、約80の死亡例が報告されています。これは clozapine による無顆粒球症による死亡例の8倍ほど上回っています。つまり、第二世代薬には「有効性」はあるものの、副作用もきわめて多いのです。また、プロラクチンに関連する副作用は、短期、長期ともに甚大な副作用であり多くの患者を悩ませています。Risperidone は顕著に血清プロラクチンを上昇させることが知られています。Risperidone はαアドレナリン受容体への親和性が高いので起立性低血圧も幾分かみられます。ただし、ヒスタミン受容体への親和性は低いため、体重増加、メタボリック・シンドローム、血糖値の調節異常は比較的少ないといえます。

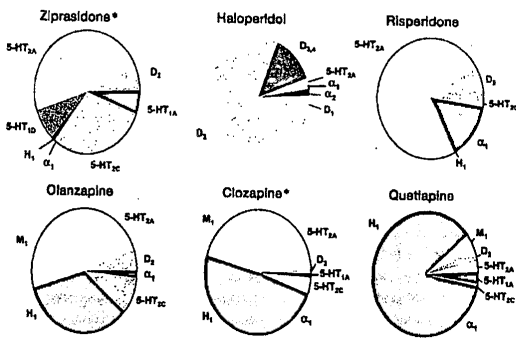


図2 各非定型抗精神病薬の受容体結合特性
Adapted from: Schmidt B. et al.: Soc. Neurosci. Abstr., 24 (2): 2177, 1998.
*: 本邦未承認

通常、治療開始から最初の数日は、臨床的な鎮静が必要である場合もありますが、長期的鎮静は患者の認知機能を損ねるおそれがあるため、良いことではありません。Risperidone は適度な鎮静作用があると思います。

Risperidone はムスカリン様コリン受容体に対する作用はきわめて軽微なため、目立った抗コリン性の副作用もありません。抗コリン性の副作用には口渇、霧視、尿閉、便秘などがあります。

さて、アメリカには精神病スペクトルの疾患治療に承認された抗精神病薬が20、世界では40あります。これら薬剤の性質が同じか、異なるのかをどのように区別すれば良いのでしょうか。

III. 第三世代薬について

Aripiprazole は第三世代薬
第三世代薬として最初の薬剤である aripiprazole は、第一世代薬の haloperidol と同じなのでしょうが、aripiprazole は第二世代である risperidone と同じでしょうか。答えは「ノー」です。

表1は、各受容体の親和性をまとめたものです。その中で、特に2つの受容体、ヒスタミン (H₁) 受容体とムスカリン性コリン (M₁) 受容体に注目して下さい。Clozapine、olanzapine はH₁受容体、M₁受容体ともに親和性がきわめて高く、quetiapine はH₁受容体との親和性はきわめて高く、M₁受容体との親和性も中程度に高いのです。

このようなことから、clozapine や olanzapine、quetiapine などを突然中止し、急速に他剤に切り替えると、いろいろな離脱症状などが出現することがあります。H₁受容体親和性が高い薬剤は、過鎮静を誘発しますが、その薬剤を突然中止する

表1 各薬剤の結合親和性

Receptors	Aripiprazole (Abilify)	Olanzapine (Zyprexa)	Risperidone (Risperdal)	Ziprasidone* (Geodon)	Quetiapine (Seroquel)	Clozapine* (Clozaril)	Haloperidol (Haldol)
D ₁	265	31	430	525	455	85	210
D ₂	0.45	11	4	5	160	126	0.7
D ₃	0.8	49	10	7	340	473	2
D ₄	44	27	9	32	1,600	35	3
5-HT _{1A}	4.4	>10,000	210	3	2,800	875	1,100
5-HT _{1B}	3.4	4	0.5	0.4	295	16	45
5-HT _{2A}	15	23	25	1	1,500	16	>10,000
α	57	19	0.7	10	7	7	6
H ₁	61	7	20	47	11	6	440
M ₁	>10,000	1.9	>10,000	>1,000	120	1.9	>1,500

The higher number denotes ↑ affinity; Arnt & Skarsfeld, 1998; Bymaster et al, 1996; Seeger et al, 1995

*: 本邦未承認

と、活動亢進や易刺激性に変化します。M₁受容体に関しては、薬剤を突然中止すると、これも離脱症状を引き起こし、急性興奮や焦燥などを引き起こすことがあります。

一方、aripiprazoleは、H₁受容体の親和性は低いため、食欲亢進、体重増加、メタボリック・シンドロームを誘発しにくい要因になっています。また、M₁受容体への親和性はほとんどありません。

IV. Aripiprazoleの臨床試験結果

1. 急性期短期臨床試験

いくつかの臨床試験結果を紹介します。いずれも統合失調症関連疾患を対象にした試験です。

図3に急性増悪入院患者を対象にした臨床試験成績を示します。これは3つの治療群、aripiprazole 20mg, 30mg, risperidone 6mgをプラセボと比較しています。ここで、aripiprazole 20mg, 30mg, risperidone 6mgのいずれも有効性が確認されました。

ついで急性増悪入院患者を対象にしたaripiprazole 15mgと30mg, haloperidolの3つの実薬をプラセボと比べた臨床試験もあります。Aripiprazoleとhaloperidolのどちらも陽性症状や陰性症状をコントロールするのに有効でした。

これらの臨床試験のデザインは各治療薬群をプラセボと比較しており、治療薬同士を比較したものではありません。ですから、この成績の意味することは、aripiprazole 15～30mgは有効、risperidoneも有効、haloperidolも有効だったということです。

2. 長期再発予防試験

こうした治療に基づき、急性期統合失調症の治療に対してaripiprazoleの承認が得られましたが、長期試験または維持治療と呼ばれる試験も実施されました。

この試験（図4）は、aripiprazoleの再発予防効果をプラセボと比較検討したもので、比較的症状の安定した患者がエントリーされていました。26週までの本試験結果から、aripiprazole 15mgで再発しなかった患者が約63%、プラセボが39%であり、有意差がありました。このことから、aripiprazoleの長期投与による有用性も確認されました。

以上のような臨床試験成績は、すでにいろいろな機会でご覧になっていることでしょう。次にアメリカでのわれわれの臨床実務にて経験しましたaripiprazoleの処方症例を4例紹介します。

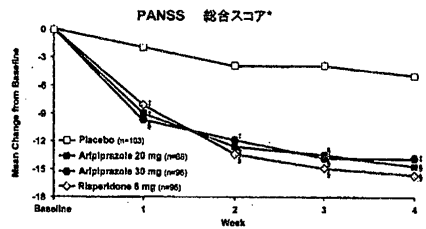


図3 Aripiprazoleとrisperidoneの精神症状に対する改善効果(プラセボとの比較)
Trial was not designed for a comparison of aripiprazole and the active comparator, risperidone.

Data from a 4-week trial (n=404) in patients with acute schizophrenia or schizoaffective disorder.

*Last observation carried forward. Mean baseline scores ranged from 91.6-94.1.

†P<0.01; ‡P<0.001 vs placebo.

Potkin et al.: Arch. Gen. Psychiatry, 60: 681, 2003.

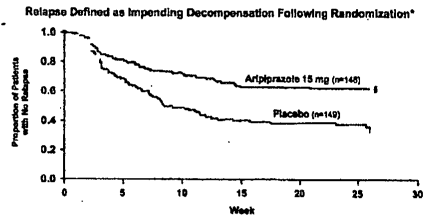


図4 Aripiprazoleとプラセボ26週間比較試験：再発予防検討

Data from a 26-week, placebo-controlled trial in patients with schizophrenia who were previously stabilized on other medications.

*Based on 1 or more of the following: a CGI-I ≥ 5 (minimally worse); a PANSS score of ≥ 5 (moderately severe) on hostility or uncooperativeness on 2 successive days; or a ≥ 20% increase in PANSS total score.

†P<0.001 vs placebo by the log-rank test. The relative risk of relapse with aripiprazole vs placebo was 0.50 (95%CI, 0.35-0.71).

Pigott et al.: J. Clin. Psychiatry, 64: 1048, 2003.

V. Aripiprazole 症例報告

1. 症例1の経緯 (図5)

症例1は19歳男性、幻覚、妄想といった多くの精神症状を呈し、ここ1～2年は学業も悪化し、典型的な統合失調症の初発例でした。最初の報告は学校からで、成績も悪く、奇異な行動をするというものでした。われわれの病院では統合失調症のどのような初発例でも、内科および精神的な総合診断の他に、CTスキャンを行っています。これは脳に腫瘍をはじめとする器質的な神経疾患があるのかどうか確認するためです。患者には統合失調症の家族歴があり、DSM-IVで妄想型統合失調症初発エピソードと診断しました。

低用量の aripiprazole 5mg から開始しました。通常、朝1回の投与を行います。このような症例の推奨用量は、5mgです。2週間に一度受診してもらい、精神症状が安定しはじめ、睡眠も非常に改善しましたが、1ヵ月後にはまだ多少幻覚が残っていました。そのような場合、2～3週間後に薬量を増量して追加反応をみます。この症例でも1日10mgまで増量し、継続して改善がみられました。最初に嘔気がみられたため、食後に服用するよう指示したところ、数週間後に嘔気が消失しました。Aripiprazole 10mgで引き続き良好で、登校できるようになり、高校を卒業し、最初の大学教職課程のためコミュニティカレッジに入学しました。必要単位の16～18単位のうち、6単位しか取れませんでした。アルバイトもしています。初回は初発エピソードの統合失調症患者としてはうまく改善したと思います。

2. 症例2の経緯 (図6)

症例2は18歳女性で、1年半の病歴があり、社会的、職業的な経歴において著しい機能異常がみられます。常に聞こえてくる幻聴に悩まされており、ここでも精神的、内科的評価を行い、統合失調症の診断が確定になりました。

患者には治療歴があり、入院歴も一度あります。Aripiprazole 10mgを連日投与し、4週間後、15mgに増量しました。消化器系の副作用がいく

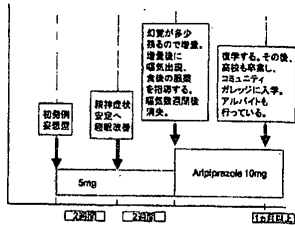


図5 症例1：19歳、男性

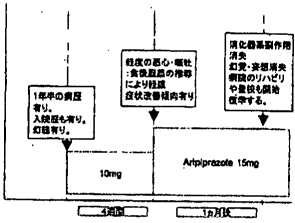


図6 症例2：18歳、女性

らかみられましたが、食後に服用するよう勧めたところ、数週間後には消失しました。幻覚や妄想は治まり、病院でのリハビリや学校でのサポートなどにより登校を開始しています。この症例でも、著しく精神症状は改善し、安定した上、復学できました。

3. 症例3の経緯 (図7)

症例3は28歳男性で、統合失調症の病歴の長いことが、最初の2例とは異なります。統合失調症歴が8年入院歴も3回ありましたが、うち1回は州立病院で、6ヵ月の入院でした。発症前から仕事をせず、約9年間働いていません。

診察した時点で、olanzapine 20mg/日、quetiapine 100mg/日が投与されていました。それでも

なお幻聴が認められ、仕事もできず、著しく悪化し、著しい体重増加や過剰な鎮静も訴えていました。ですから、基本的にはただ家にいて、寝ているだけの状態でした。著しい過鎮静と体重増加がみられ、この1年で糖尿病または血糖値異常を発症していました。そこで、aripiprazole 10mg/日の投与を開始しましたが、olanzapineとquetiapineの用量は変更していません。Aripiprazole 10mgを追加しただけです。その時（ベースライン）の血糖値を調べたところ、絶食時血糖値は190mg/dl、BMIは28で、著しい異常値でした。さらに2週間後、aripiprazoleの用量を15mgに増量し、olanzapineの用量を20mgから15mgに減量し、

quetiapineを50mgに減量しました。さらに2週間後、aripiprazoleを20mgに増量し、quetiapineを中止し、olanzapineを5mgに減量しました。急速にスリッパングするのではなく、約4週間かけてこの段階にもっていききました。そしてさらに2週間後、aripiprazole 20mgを継続したまま、olanzapineを中止しました。2週間に1回経過観察のため通院しています。この3～4ヵ月経過を観察していますが、BMIが著しく低下し、血糖値も正常値（110mg/dl）になり、現在は昼間のリハビリプログラムに参加し、コンピューター訓練のクラスにも参加しています。QOLと副作用プロファイルに著しい改善がみられ、特に認知機能において、以前より優れた効果が認められています。

4. 症例4の経緯 (図8)

症例4は治療に長期間かかった本当に難しい症例でした。症例4は32歳、白人男性で、慢性的な統合失調症の診断でした。最初の精神科エピソードは17歳の時でした。この患者には幻聴、妄想、きわめて強迫的な思考、トランスなど多くの症状が認められました。こうした症状は緊急性であると判断しました。患者は5分くらい見上げていただけだった。じっとしてたりして、家族はそれが発作だと考えていましたが、私は緊

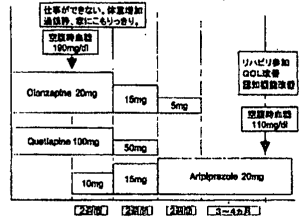


図7 症例3：28歳、男性

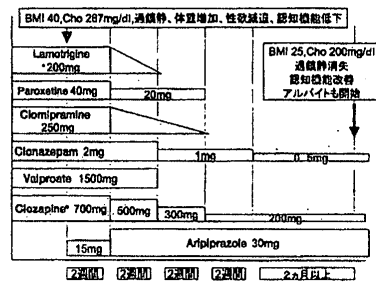


図8 症例4：32歳、男性

＊：本邦未承認

強症状に近いものだと考えています。うつ状態、陰性症状、動機づけの欠如、機能的障害と言えると思います。何度も入院し、デイホスピタルのような日帰り入院を行っても、依然、著しい機能不全状態を呈しました。

この患者は著しい多剤併用でした。まず clozapine 700mg があります。Lamotrigine 200mg（日本では未承認）はうつ症状のためです。Clomipramine 250mg は強迫症状のためです。Clonazepam 0.5mg × 4 は不安症状のためです。Paroxetine 40mg はうつ症状、valproate 500mg × 3 は気分安定薬の一種で、興奮・焦燥のためです。9 年間にわたり、あらゆるターゲット症状に対して、種々の薬剤を投与されてきました。そのため、患者がこうした薬剤すべてを必要としないと考え、患者を薬剤から解放する必要があります。患者はこれらの薬剤から、過剰な鎮静、体重増加、性欲減退、認知機能障害などの副作用を生じていました。もちろん、カルテ、つまり精神療の記録をすべて取っており、なぜ、こうした薬剤をこの患者に投与しなければならなかったのか把握していました。コレステロール値がきわめて高く、メタボリック・シンドロームもみられ、BMI は 40 でした。これはご存知のように clozapine が著しい体重増加を誘引したためです。

この患者に aripiprazole 15mg の投与を開始しましたが、clozapine、lamotrigine、clomipramine、paroxetine の用量は変更せず、そのままにして、aripiprazole を追加しました。2 週間後、clozapine を 500mg に減量し、aripiprazole を 30mg に増量し、lamotrigine、clomipramine の減量を開始し、paroxetine は 40mg から 20mg に減量しました。その 2 週間後、clozapine を 300mg に減量し、lamotrigine と valproate の投与を中止し、paroxetine を継続しながら、ベンゾジアゼピン系の clonazepam を少量継続しました。それから、clozapine を 200mg に減量し、clomipramine の投与を中止し、必要に応じて clonazepam を継続しました。Aripiprazole 30mg を継続して、2 週間後、clozapine を 200mg に、clonazepam を 0.5mg / 日に減量しました。

この後 4 ～ 6 ヶ月服用してから、再度 cloza-

表 2 Aripiprazole 使用経験からの提言

- 1) 10～30mg のいずれの用量でも有効。
- 2) 個々の患者の用量は、その患者の症状・状態により異なる。
- 3) 適切なスイッチング方法を見出すことがポイント。
- 4) その患者の至適用量を見出すことが、最も重要なポイント。
- 5) Aripiprazole の副作用はきわめて軽微である。

pine を 100mg に減量するか、完全に中止することになると思いますが、この患者はきわめて慢性の患者ですから、性急に中止したくはありません。現在は 2 種類の薬剤のみ、つまり、clozapine をごく少量と aripiprazole で安定しています。患者は引き続き快方に向かっており、BMI は低下し、コレステロール値も低下し 200 未満でした。過剰な鎮静はみられず、認知機能も改善しました。鎮静だけでなく、clozapine の抗コリン作動性の副作用も有意に減少しました。この 2 ヶ月間は安定しており、現在は地域のコミュニティカレッジに入学し、ファーストフード店でアルバイトをしています。その仕事はそれほどハードなものではありませんが、このような重い病気を抱えていた 1 人の患者が、社会復帰まで達した有効例になります。

VI. ま と め

1. Aripiprazole 使用経験からの提言

以上のことから言えることは（表 2）、aripiprazole は 10～30mg のいずれの用量でも有効でした。現在では、5 mg 投与も行っています。他剤では、一定の用量に達しないと効果がみられないことがありますが、aripiprazole はどの用量でも有効と言えます。

すべての用量が有効ということは、患者全体に 5 mg 投与から開始するのか、30mg 投与から開始するのかという疑問がでます。高用量から開始するのか、低用量から開始するのかの判断は、やはり臨床経験やいろいろな情報の蓄積によるところが大きいと思います。臨床経験からいう

と、低用量に反応する患者もいれば、高用量に反応する患者もいるからです。臨床医として常にそうしたことに気づき、考慮しながら、切り替えや、用量も考えていくことが必要です。

Aripiprazole による活動亢進について述べます。活動亢進は必ずしも悪いということではないのです。実際、陰性症状の強い患者には良いことが多いのです。部屋にこもりきりで、どこにも出かけず、誰とも話さない患者には、活動を活性化させる必要があります。過剰な活動亢進には通常ベンゾジアゼピンが有効で、aripiprazole の投与量を上げることでも有効と言えるでしょう。

アカシジアと活動亢進は似たような症状を示します。アカシジアには用量を下げたいし、賦活には用量を上げたいところです。このため、このアカシジアと活動亢進を明確に区別しなければなりません。私は、椅子に座っている患者に、「内面的に落ちつかず、不安ですか」と尋ねます。「イエス」と答えた患者には、アカシジアが多いのではと判断しています。Aripiprazole は陰性症状および認知機能にも改善がみられると言います。過剰の鎮静をかけますと、かえって陰性症状や認知機能は悪化します。ドパミン・パースナルアゴニストである aripiprazole は、何となく従来薬とは効き方が違います。これは、ドパミンを完全に遮断しないことによると思います。Aripiprazole を投与した多くの患者から「まだ完全に精神症状がコントロールされる前から、今までの薬剤とは効きかたが違うなという感じがします」と言われます。Aripiprazole のドパミン・システムスタビライザーから来る、いわゆるウェルビーイングの質の違いなのかもしれません。

2. Aripiprazole へのスイッチング方法について

表 3 は aripiprazole の治療アルゴリズムの 1 つで、私が提示したものです。低用量である 5 ～ 10 mg で投与を開始し、2 週間は従来薬を継続してもらおう一方、その後 15mg に増量すると共に、従来薬を減らし 2 ～ 4 週間かけて減量していきます。

頻度はそれほど多くはありませんが、軽度から中等度の一過性の悪心・嘔吐がみられます。また、

表 3 スwitching 方法について（Aripiprazole の使用経験から）

- ・ Aripiprazole 10mg（できるだけ低用量）から開始。
- ・ 最初の 2 週間は、従来薬に追加して様子を見る。
- ・ 3 週目から、aripiprazole を 15mg まで増量し、従来薬（抗精神病薬）を徐々に減量していく。
- ・ 少なくとも 2 ～ 4 週間は、その状態で経過を追う。
- ・ どの程度まで従来薬を減らすかは、その患者の状態にもよる。Clozapine の場合などは、さらに時間をかけて漸減し、100～200mg をそのまま継続することもある。

アカシジアも出現しますが、3 ～ 4 週間以内に 50% 程度に軽減されます。アカシジアには、β 遮断薬を投与します。悪心や嘔吐には制吐薬を投与するか、aripiprazole を食後間もなく服用してもらうように指導します。Aripiprazole は就寝時ではなく、よく日中に投与します。ドパミン・パースナルアゴニストは、睡眠を誘導するような作用は少ないと考えているからです。このため、通常は鎮静作用を期待しない方がいいでしょう。確かに、aripiprazole の高用量では鎮静作用も出てきます。Aripiprazole で鎮静作用が出現した場合は、午前中の投与から就寝前投与に切り替えるのも良い方法です。

さらに大事なことは、前薬中止に伴うリバウンド症状を防ぐことです。リバウンド症状と精神症状を混同すべきではありません。患者個々の長期をとらえた有効性を、その患者への有効性と最小限の副作用から見つけ出すことです。Aripiprazole の臨床試験では 15mg から投与開始しているからといって、やみくもに 15mg から開始するのではなく、最大の有用性を得ると考えられるその患者の最適な用量をみつける作業が必要になってきます。もちろん断片的な徴候と、臨床試験によって示される治療に属する知識や、こうした患者を治療してきた何年もの経験から得られる治療に関する知識を組み合わなければなりません。

以上が、私がこれまでに経験したいくつかの事例から確信することになったことです。どうもありがとうございました。

Abridged English translation of Rinsyou seisin yakuri (Japanese Journal of clinical psychopharmacology), 9, 2503-2511, 2006

<From left column on page 2504, line 3 from the bottom to left column on page 2506, line 9>



II. Second Generation Drugs

Efficacy and Utility

These drugs (Figure 2) are second generation drugs, starting with clozapine. Many of second generation drugs are efficacious for the treatment of positive and negative symptoms, but have very problematic side effects. For example, clozapine is not approved in Japan still now due to its side effects. Discussions on the action of an antipsychotic drug are mostly on its "efficacy". Also, most of the test results which pharmaceutical companies provide us are on "efficacy", but not on "utility". We consider that "utility" involves not only "efficacy", but also "safety/tolerability", and refers to the most desirable treatment for the patient. It is because a patient will stop taking even a very prominent therapy for the certain patient if the therapy has too many side effects, and it will lose its "utility".

As for second generation drugs, they are decreased in "utility", apparently because of their side effects. Clozapine, as well as other drugs, causes various side effects, such as weight gain and metabolic syndrome. In metabolic syndrome the risk of the cardiotoxicity, the prevalence of cardiac disease, and/or the mortality are increased by 4-10 times. Additionally, approximately 80 death cases so far have been reported for diabetic ketoacidosis secondary to diabetes due to clozapine and olanzapine. This is about 8 times more of the death cases from

agranulocytosis due to clozapine. In short, second generation drugs have "efficacy", but with very many side effects. Moreover, side effects related to prolactin are severe both in short- and long-term, and afflict many patients. Risperidone is known to raise serum prolactin markedly. Because risperidone has high affinities to α_1 adrenergic receptors, also orthostatic hypotension is observed to some extent. On the other hand, risperidone has low affinities to histamine receptors, thus it is considered to have a relatively little weight gain, metabolic syndrome, and abnormal regulation of blood glucose levels.

Generally, clinical sedation may be necessary for several days from the beginning of the therapy. A long-term sedation is not good because it may impair cognitive functions of the patient. Risperidone is considered to have a moderate sedative effect.

Because risperidone has very slight effects on muscarinic choline receptors, it does not cause any prominent anticholinergic side effects. Anticholinergic side effects include dry mouth, misty vision, urinary retention, and constipation.

Currently, there are 20 antipsychotic drugs approved for the treatment of diseases of the psychosis spectrum in the United States, and 40 antipsychotic drugs in the world. How should we distinguish the properties of these drugs, if they are same or not?

III. Third Generation Drugs

Aripiprazole is a third generation drug.

Is aripiprazole, which was firstly launched as third generation drug, same as haloperidol which is a first generation

drug? Or, is aripiprazole same as risperidone, a second generation drug? The answers are "no".

Table 1 shows the affinity of each receptor. Among them, two receptors, histamine (H_1) receptor and muscarinic choline (M_1) receptor, are to be noted. Clozapine and olanzapine have very high affinities for both of H_1 receptor and M_1 receptor, while quetiapine has a very high affinity for H_1 receptor, and also a moderately high affinity for M_1 receptor.

Thus, abrupt withdrawal of clozapine, olanzapine, quetiapine or the like and rapid switching to other drugs may lead to various withdrawal symptoms. Drugs with a high affinity for H_1 receptor induce hypersedation, but it may change into hyperactivity and/or irritability after an abrupt withdrawal of said drugs. As to M_1 receptor as well, an abrupt withdrawal of the drug may cause withdrawal symptoms, and may cause acute excitement and/or irritation.

On the other hand, aripiprazole has a low affinity for H_1 receptor, which is a reason that it is less likely to cause bulimia, weight gain, and/or metabolic syndrome. Additionally, aripiprazole has little affinity for M_1 receptor.

[Figure 1]

Dopamine D₂ receptor partial agonists

- In the state where the dopamine neurotransmission is excessively activated, they act as antagonists (amelioration of positive symptoms).
- In the state where the dopamine neurotransmission is excessively lowered, they act as agonists (reduction of occurrence of EPS).
- Serotonin 5-HT_{1A} receptor partial agonist
- Serotonin 5-HT_{2A} receptor partial agonist



Dopamine system stabilizer (DSS)

Figure 1 Pharmacological properties of Aripiprazole

[Figure 2]

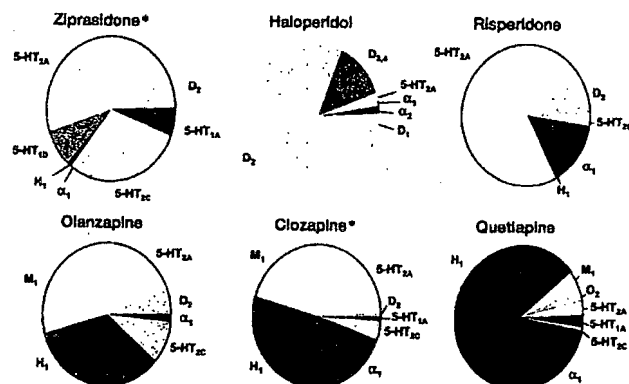


Figure 2 Receptor binding properties of various atypical agents

Adapted from : Schmidt B. et al. : Soc. Neurosci. Abstr., 24 (2): 2177, 1988.

*: Yet to be approved in Japan

[Table 1]

Table 1 Binding affinities of various atypical agents

Receptors	Aripiprazole (Abilify)	Olanzapine (Zyprexa)	Risperidone (Risperdal)	Ziprasidone* (Geodon)	Quetiapine (Seroquel)	Clozapine* (Clozaril)	Haloperidol (Haldol)
D ₁	265	31	430	525	455	85	210
D ₂	0.45	11	4	5	160	126	0.7
D ₃	0.8	49	10	7	340	473	2
D ₄	44	27	9	32	1,600	35	3
5-HT _{1A}	4.4	>10,000	210	3	2,800	875	1,100
5-HT _{1B}	3.4	4	0.5	0.4	295	16	45
5-HT _{2C}	15	23	25	1	1,500	16	>10,000
α ₁	57	19	0.7	10	7	7	6
H ₁	61	7	20	47	11	6	440
M ₁	>10,000	1.9	>10,000	>1,000	120	1.9	>1,500

The higher number denotes ↑ affinity ; Arnt & Skarsfeld, 1998 ; Bymaster et al, 1996 ; Seeger et al, 1995

*: Yet to be approved in Japan

ANEXO 2

Atypicality of Atypical Antipsychotics

Andrew Farah, M.D.

Objective: To review the current definition of *atypicality*, discuss the unique features of each atypical antipsychotic, and determine whether the available drugs in this class really meet the classical definition of *atypicality*.

Data Sources: A PubMed search was conducted to identify literature on the subject of this review, supported by additional articles based on the author's clinical knowledge and experience.

Study Selection and Data Extraction: Relevant references were extracted and summarized in order to meet the objective of the article.

Data Synthesis: Atypical antipsychotics are considered a major advance over conventional antipsychotics, primarily because they offer effective treatment alternatives that are relatively free of extrapyramidal symptoms. In fact, the term *atypicality* was originally used to describe antipsychotic agents with a minimal risk of causing extrapyramidal symptoms. However, over the years the definition has been modified such that there is currently no consensus on a true definition of *atypicality* for these agents. Each of the atypical antipsychotics (clozapine, risperidone, olanzapine, quetiapine, ziprasidone, and aripiprazole) commercially available in the United States is unique in terms of its pharmacologic profile, differing with respect to receptor-binding affinity, mechanism of action, and adverse events. Of the available atypical antipsychotics, clozapine and quetiapine have shown the lowest propensity to cause extrapyramidal symptoms. Although the risk of extrapyramidal symptoms is lower with risperidone and olanzapine than with conventional antipsychotics, risk increases with dose escalation. Data for ziprasidone indicate that the risk of extrapyramidal symptoms may be similar to that of risperidone and olanzapine. There is a concern of akathisia with aripiprazole; however, more experience with this agent is needed before definitive conclusions are made.

Conclusion: If the definition of "atypical" antipsychotic is considered to be freedom from extrapyramidal symptoms, then, based on a comprehensive review of available data and clinical experience, clozapine and quetiapine appear to be the only true atypicals.

(*Prim Care Companion J Clin Psychiatry* 2005;7:268-274)

The development of atypical antipsychotics was an important milestone in the history of psychiatry, because it brought effective treatment options with a reduced risk for adverse events. In particular, the atypical antipsychotics appear to be much less likely to cause extrapyramidal symptoms (EPS), a group of movement disorders associated with physical disability and subjective discomfort and distress, including parkinsonism, akathisia, dystonia, and tardive dyskinesia (a long-term manifestation of EPS).¹

Atypical antipsychotics were originally defined by a reduced risk of EPS as an adverse event. However, as more atypical antipsychotic agents were introduced, marketing efforts and recent literature modified the definition. Furthermore, it is now unclear whether atypicality should be a clinical distinction (related to EPS or negative symptom relief), a chemical distinction (receptor profile), or a mixture of both.

The purpose of this article is to review the current definition of *atypicality*, discuss the unique features of each atypical antipsychotic, and determine whether the available drugs in this class really meet the classical definition of *atypicality*. A PubMed search was conducted to identify literature on the subject of this review, supported by additional articles based on the author's clinical knowledge and experience. Relevant references were extracted and summarized in order to meet the objective of the article.

DEFINITION OF ATYPICALITY

There is currently no consensus on a true definition of *atypicality* for antipsychotic medications. Originally, the term was used to describe effective antipsychotic agents associated with a minimal risk of causing EPS.^{2,3} However, as described in reviews by Markowitz et al.² and Goldstein,⁴ a broader definition of *atypicality* is used today. In addition to a reduced risk of EPS, other elements thought to contribute to atypicality include the following: transient elevation in prolactin levels, efficacy in treating both positive and negative symptoms of schizophrenia, a mechanism of action that involves serotonin (5-HT)-2A and -2C antagonism and/or mesolimbic specificity over nigrostriatal dopamine neurons, and efficacy in treatment-resistant schizophrenia.^{2,4} At times, various combinations of these descriptions have served to define *atypicality*.

Several types of dopamine receptors exist in various regions of the human brain (Table 1).⁵ Psychosis is be-

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Table 1. Dopamine Receptors^a

Receptor Type	Location
D ₁	Cortex and basal ganglia
D ₂	Striatum
D ₃	Limbic region
D ₄	Limbic region

^aBased on Beng-choon et al.⁵

lieved to result from excess dopamine in the mesolimbic and/or mesocortical regions of the brain, but blockade of dopamine in the striatum of the brain can result in adverse events, such as parkinsonian symptoms and hyperprolactinemia.^{6,7} All clinically effective antipsychotics at least partially antagonize the dopamine-2 (D₂) receptor. However, the degree of D₂-receptor affinity differs and is thought to serve as a predictor of adverse events such as EPS (including akathisia).^{4,8} Data from positron emission tomography (PET) studies evaluating D₂ occupancy by antipsychotics indicate that thresholds of 65%, 72%, and 78% are associated with clinical efficacy, hyperprolactinemia, and EPS, respectively.⁹

All antipsychotics launched after clozapine have been categorized as atypical, regardless of their D₂ affinity or propensity to cause EPS, although not all compounds so classified meet the aforementioned criteria of transient prolactin elevation, 5-HT-2A and -2C antagonism, mesolimbic specificity, and efficacy in treating positive and negative symptoms and in treatment-resistant schizophrenia.

→ Unlike classes of medication such as conventional antipsychotics or serotonin reuptake inhibitors, antipsychotics categorized as atypical do not share, even in a broad sense, the same general pharmacologic profile as other members of their class. For example, the atypical antipsychotics differ with respect to receptor-binding affinity (Table 2),¹⁰⁻¹³ proposed mechanism of action, and adverse event profile.

ATYPICAL ANTIPSYCHOTICS

There are 6 atypical antipsychotics commercially available in the United States: clozapine, risperidone, olanzapine, quetiapine, ziprasidone, and aripiprazole. Compared with the conventional antipsychotics, the atypicals have a lower propensity to induce EPS and tardive dyskinesia and have a broader spectrum of efficacy (e.g., greater improvements in negative, depressive, and cognitive symptoms).¹⁴ In a review of 11 long-term antipsychotic trials lasting at least 1 year,¹⁵ the weighted mean annual incidence risk of tardive dyskinesia was 2.1% among patients receiving an atypical antipsychotic regardless of age group compared with 5.4% for adult patients receiving haloperidol (3 studies, mean dose = 13.1 mg/day). The estimated risk of tardive dyskinesia among individual atypical antipsychotics varied, with reported rates of 0% to 0.5% for olanzapine (2 studies, mean dose = 13.6 mg/day), 0.6% to 0.7% for risperidone (5 studies, mean dose = 2.7 mg/day

orally or 55.2 mg/14 days intravenous) and quetiapine (2 studies, mean dose = 408.3 mg/day), and 6.8% for ziprasidone (1 study, mean dose = 92 mg/day).

Differences exist between the atypicals with regard to weight gain, hyperprolactinemia, sedation, sexual dysfunction, and anticholinergic and metabolic adverse events. The effects of antipsychotic treatment on the development of metabolic disorders are gradually emerging. Currently, warnings about hyperglycemia and diabetes mellitus are contained in the U.S. prescribing information for each of these agents.^{10,11,16-19} Cerebrovascular adverse events were first reported with risperidone.²⁰ However, a warning regarding cerebrovascular adverse events in patients with dementia-related psychosis was recently added to the U.S. prescribing information for aripiprazole, olanzapine, and risperidone.^{10,17,19} The following sections discuss the differences with regard to atypicality among these agents.

Clozapine

Clozapine was the first atypical antipsychotic approved for use in the United States, although it is now reserved for severely ill patients with schizophrenia and those with schizophrenia or schizoaffective disorder at risk for suicidal behavior.¹⁶ It is classified as a dibenzothiazepine derivative and is known to be particularly effective in patients who do not respond to conventional or other atypical antipsychotics.^{16,21} The effective dosage range is 300 to 600 mg/day, but dosages of up to 900 mg/day may be needed in some patients.¹⁶

Clozapine fits all of the proposed definitions of *atypicality*. It has a low propensity for causing EPS after acute administration, does not produce tardive dyskinesia with long-term administration, and does not elevate plasma prolactin levels.⁴ Imaging studies have shown a correlation between negative symptoms and reduced prefrontal blood flow²² and glucose metabolism.²³ In a report of a patient with first-episode schizophrenia, clozapine was shown to reverse hypofrontality, which may be the mechanism by which negative symptoms are improved.²²

The affinity of clozapine for D₂ receptors is below the threshold that is predictive of EPS and hyperprolactinemia. At doses of 125 to 600 mg, clozapine has a D₂ occupancy of 20% to 67%,²⁴ although dissociation appears to be rapid.²⁵ In addition to D₂ receptor blockade, clozapine shows high affinity for D₁ receptors and antagonism for D₃ and D₄ subtypes.²⁶ Although activity at these receptors is not characteristic of atypicality, it may be important for antipsychotic activity²⁶ (although quetiapine is an effective antipsychotic that has virtually no affinity for D₄ receptors). Data from Nordstrom et al.²⁴ indicate that at doses of 300 to 600 mg, clozapine has a D₁ occupancy of 33% to 59%. The affinity of clozapine for 5-HT receptors is also high, with a 5-HT₂ receptor occupancy of 84% to 94% at doses of 125 to 400 mg.²⁴

Table 2. In Vitro Receptor-Binding Profiles of the Atypical Antipsychotics ^{a,b}						
Receptor	Clozapine (K _i , nM)	Risperidone (K _i , nM)	Olanzapine (K _i , nM)	Quetiapine (IC ₅₀ , nM)	Ziprasidone (K _i , nM)	Aripiprazole (K _i , nM)
D ₁	85	75	31	1268	—	—
D ₂	125	3	11	329	4.8	0.34
5-HT _{1A}	770	490	> 1000	717	3.4	1.7
5-HT _{1D}	980	100	800	—	2	—
5-HT _{2A}	12	0.6	4	148	0.4	3.4
5-HT _{2C}	8	26	11	—	1.3	15
α ₁	7	2	19	94	10	57
H ₁	6	155	7	30	47	61
M ₁	1.9	> 10,000 ^c	1.9	> 10,000	> 10,000 ^c	> 1000 ^c

^aData from Bristol-Myers Squibb Company,¹⁰ Pfizer Inc.,¹¹ Bymaster et al.,¹² and Goldstein.¹³
^bDashes indicate data not presented.
^cIC₅₀.
Abbreviations: 5-HT = serotonin, α₁ = α₁-adrenoceptor, D₁ = dopamine-1, D₂ = dopamine-2, H₁ = histamine-1, IC₅₀ = concentration that inhibits 50%, K_i = inhibition constant, M₁ = muscarinic-1, nM = nanomolar.

The use of clozapine is primarily limited by the risk of agranulocytosis, defined as a granulocyte count of < 500/mm³.²¹ Data collected from more than 11,000 patients through the Clozaril Patient Management System indicate that the incidence of agranulocytosis was 0.80% at 1 year.²⁷ In general, agranulocytosis appears to occur within the first 3 months of therapy, with the risk peaking by the third month.²⁷ Gaszner et al.²⁸ reported a prevalence of 1% for granulocytopenia and 0.26% for agranulocytosis among a group of 750 patients who received clozapine therapy for schizophrenia or schizoaffective psychosis over a period of 15 years. These authors suggest that, with proper management, blood dyscrasias induced by clozapine appear to be reversible and not life threatening.

Other adverse events of significant concern in patients receiving clozapine include weight gain, risk of seizures, myocarditis, pancreatitis, and orthostatic hypotension with or without syncope. With regard to weight, a meta-analysis evaluating 10 weeks of therapy with 4 of the 6 commercially available atypical antipsychotics showed a mean increase in weight of 4.45 kg with clozapine, the greatest increase among the atypicals studied.²⁹ Myocarditis appears to be a rare but serious adverse event.³⁰ Postmarketing data for clozapine indicate that the risk of myocarditis appears to be greatest during the first month of therapy but may occur at other times.¹⁶ In an analysis of an international database on adverse drug reactions maintained by the World Health Organization, examination of the relationship between antipsychotics and myocarditis and cardiomyopathy using Bayesian statistics suggests that these symptoms are strongly associated with clozapine use.³¹ As a result, it is recommended that clozapine be promptly discontinued in patients suspected of having myocarditis.

Risperidone

Risperidone is classified as a benzisoxazole derivative and is indicated for the treatment of schizophrenia and acute manic or mixed episodes associated with bipolar disorder.¹⁷ It is widely used and is effective, along with its pri-

mary metabolite 9-hydroxyrisperidone. The dosage range for risperidone is 2 to 16 mg/day. Based on clinical experience, the majority of responders require 6 mg/day or less of risperidone.

Of the atypical antipsychotics, risperidone is the weakest in terms of atypicality criteria. Although early clinical studies with risperidone indicated that the incidence of EPS is not greater than that seen with placebo, this may not be the case. Dose-dependent EPS have been reported in 60% to 70% of patients taking risperidone at dosages of ≥ 6 mg/day.³ In a prospective study of 350 antipsychotic-naïve patients, those treated with low-dose risperidone had a similar high incidence of movement disorders as those who received low-dose haloperidol.³² Numerous case reports of dystonic reactions and tardive dyskinesia with risperidone also have appeared in the literature.³³⁻⁴⁰ In addition, risperidone is more likely than other atypicals to cause persistently elevated prolactin levels.^{4,41,42} Risperidone also is associated with a moderate risk of weight gain (1.69–2.51 kg) following 10 weeks of treatment²⁹ and orthostatic hypotension and a mild risk of somnolence.¹⁴

In a study of D₂ occupancy in individuals receiving risperidone doses of 2, 4, and 6 mg, the mean level of D₂-receptor occupancy was 66% at 2 mg, 73% at 4 mg, and 79% at 6 mg.⁴³ D₂-receptor occupancy of risperidone at doses of ≥ 4 mg is above the threshold associated with EPS and hyperprolactinemia.^{43,44} Risperidone is able to occupy D₂ receptors gradually, which is not a property shared with the conventional antipsychotics or olanzapine.⁴⁵ Occupancy of 5-HT₂ receptors has been shown to be > 95% with risperidone at dosages of 2 to 4 mg/day.⁸

Olanzapine

Olanzapine belongs to the thienobenzodiazepine class of psychotropic agents. It is indicated for the treatment of schizophrenia and is currently the only atypical antipsychotic approved for use in both acute and maintenance therapy of mixed or manic episodes associated with bi-

polar I disorder.¹⁹ The approved dosage range of olanzapine is 10 to 15 mg/day for schizophrenia and 5 to 20 mg/day for bipolar disorder.

The atypicality of olanzapine is questionable and appears to fall between that of clozapine and risperidone. Olanzapine generally has a mild-to-minimal risk of causing EPS and hyperprolactinemia¹⁴; however, the risk is dose-dependent. In a study evaluating the D₂ and 5-HT₂ occupancy of olanzapine,⁴⁶ EPS and hyperprolactinemia were noted to occur in patients treated with olanzapine at dosages of > 20 mg/day. In this study, D₂ occupancy was 55% at 5 mg/day, 73% at 10 mg/day, 75% at 15 mg/day, 76% at 20 mg/day, 83% at 30 mg/day, and 88% at 40 mg/day. The 5-HT₂ receptor occupancy was greater than 90% at all olanzapine doses studied.

With the exception of clozapine, olanzapine has been associated with a higher degree of weight gain than other available atypical antipsychotics.^{14,47} At 10 weeks, olanzapine at standard doses may produce between 4 and 4.5 kg of weight gain. Weight gain with olanzapine does not appear to be dose related within the therapeutic dosage range of 5 to 20 mg/day, and weight changes tend to plateau at 7 to 8 kg after about 40 weeks of treatment.⁴⁷ Olanzapine is also associated with a moderate risk of transient somnolence.¹⁴ Unlike the other atypical antipsychotics, the oral clearance of olanzapine is increased by smoking (cytochrome P450 1A2 [CYP1A2] inducers) and may require dosage adjustments in some patients.¹⁹ This is a significant interaction, given that different surveys have shown that 58% to 90% of patients with schizophrenia smoke (vs. 28%–30% of the general U.S. population).⁴⁸

Quetiapine

Quetiapine is similar in structure to clozapine (but derived from perlapine) and as such is classified as a dibenzothiazepine derivative. It is indicated for the treatment of schizophrenia and acute manic episodes associated with bipolar I disorder.¹⁸ The clinically effective dosage range for both bipolar I disorder and schizophrenia is 400 to 800 mg/day, although more severe cases may require higher dosages.

Clinical data indicate that quetiapine is associated with levels of EPS similar to those of placebo across the dosage range and is not associated with elevations in prolactin levels.^{4,49} It has been suggested that the atypicality of quetiapine may be explained by its ability to transiently occupy D₂ receptors.⁴ This characteristic, unique only to quetiapine and clozapine, permits modest occupancy at the D₂ receptors that rapidly declines to minimal levels 12 to 24 hours after the last dose.^{4,25,50} Like clozapine, quetiapine has a higher relative affinity for 5-HT_{2A} receptors than D₂ receptors. In a PET imaging study evaluating the D₂ and 5-HT₂ occupancy of quetiapine at dosages of 150 to 600 mg/day, quetiapine was found to have minimal D₂ occupancy (0%–27%) and high 5-HT₂ occupancy

(19%–94%) 12 hours after the last dose.⁵⁰ Thus, the low D₂ occupancy of quetiapine combined with its ability to transiently occupy these receptors may explain the very low risk of EPS with this agent.⁴ Antipsychotic effects are achieved with rapid but transient binding (58%–64% D₂ occupancy at 2–3 hours after a dose, declining to minimal occupancy by the end of a 12-hour dosing interval).⁵⁰ This transient binding appears to be sufficient for clinical efficacy of quetiapine,⁵⁰ while never approaching the 78% threshold of D₂ occupancy necessary for EPS.

Quetiapine has a greater affinity for α_1 -adrenergic and histamine-1 receptors than for D₂ receptors. As a result, patients taking quetiapine may be at risk for orthostatic hypotension and transient sedation.⁴ In clinical practice, the risk of sedation appears to be greater than that of orthostatic hypotension, provided patients are appropriately monitored. In a retrospective analysis of the quetiapine safety database consisting of data from 77 clinical studies, 25.5% of patients (2013/7894) reported somnolence at least once during quetiapine therapy.⁵¹ In this analysis, somnolence was of mild intensity and occurred in the first week of therapy, with a decrease over time such that, by week 4, the first onset of somnolence was reported in < 1% of patients receiving the medication. Quetiapine has been reported to be associated with a 1.58-kg mean increase in weight following 9 to 13 weeks of therapy.⁵²

Ziprasidone

Ziprasidone is a structural analog of risperidone and as such is classified as a benzisoxazole derivative. It is indicated for the treatment of schizophrenia and acute manic or mixed episodes associated with bipolar disorder with or without psychotic features.¹¹ The effective dosage range for ziprasidone is 80 to 160 mg/day. In our clinical experience with this medication, only about one quarter of patients are responsive; however, because of its ability to antagonize 5-HT_{1A} and its high affinity for other 5-HT receptors, it has the potential to reduce depressive symptoms.⁴

Controlled clinical trials suggest that ziprasidone is associated with a low risk of EPS and transient but non-dose-related elevations in prolactin.^{53–55} However, anecdotal experience suggests that the occurrence of EPS during ziprasidone therapy may be more prominent than clinical trials indicate. Unlike clozapine or quetiapine, ziprasidone has a high affinity for D₂ receptors and a very high affinity for 5-HT₂ receptors.⁴ Despite the high affinity for D₂ receptors, it has been suggested that its higher affinity for 5-HT_{2A} receptors may limit the occurrence of EPS.⁵⁶

In a PET study evaluating the D₂ and 5-HT₂ receptor occupancy of ziprasidone at dosages of 40, 60, 80, and 160 mg/day,⁵⁷ the mean 5-HT₂ receptor occupancy (76%; range, 52%–99%) was significantly higher than the mean D₂ receptor occupancy (56%; range, 10%–73%). Because the relationship between D₂ and 5-HT₂ receptor occupancy

and plasma ziprasidone levels was significantly positively correlated, the authors were able to predict that the maximum D₂ receptor occupancy of ziprasidone would be 84%. These findings suggest that the relatively high D₂ occupancy (maximum 73%; predicted maximum 84%) observed with ziprasidone in this study is more similar to that of risperidone and olanzapine than that of clozapine and quetiapine.

Ziprasidone has been reported to be associated with a mild risk of orthostatic hypotension, sedation, and QT prolongation.¹⁴ Concern over QT prolongation and the risk of sudden death was a significant issue for ziprasidone when it was first approved to market and led to numerous investigations of the cardiac safety of antipsychotics. Although a warning for QT prolongation and risk of sudden death remains in the product label for ziprasidone,¹¹ excessive concern appears to be unfounded.⁵⁸ QTc interval change occurs with countless psychotropic medications and on the whole is minimal, highly variable from patient to patient, and only of major concern in cardiac patients and those already taking agents known to prolong QTc. Although data with ziprasidone are limited, weight gain appears to be minimal (0.04 kg) over the course of 10 weeks,²⁹ and ziprasidone is associated with a small loss in weight indistinguishable from that seen with placebo over the course of 1 year.⁵⁹

Aripiprazole

→ Aripiprazole differs from the other atypical antipsychotics in that it is a partial agonist at D₂ and 5-HT_{1A} receptors and has antagonistic activity at 5-HT_{2A} and 5-HT_{2C} receptors.^{60,61} It is indicated for the treatment of schizophrenia and acute manic and mixed episodes associated with bipolar disorder and has an effective dosage range of 10 to 30 mg/day.^{10,62,63}

Clinical data suggest that the occurrence of EPS with aripiprazole is similar to that with placebo, and it does not appear to elevate prolactin levels.^{10,60} However, EPS and akathisia have been reported to occur during aripiprazole therapy.^{10,64,65}

In a PET study evaluating aripiprazole 0.5 to 30 mg/day in 15 healthy subjects, a dose response in D₂- and D₃-receptor occupancy was found. Receptor occupancy increased from below 40% at 0.5 mg to over 90% at 30 mg/day.⁶⁶ These results suggest that administration of high doses of aripiprazole would lead to an increased risk of EPS; however, no EPS were observed in patients receiving high doses (30 mg/day) of aripiprazole in this study. The authors suggest that the lack of EPS may have to do with the partial agonistic activity of aripiprazole.⁶⁶ However, in clinical trials evaluating aripiprazole for the treatment of schizophrenia and bipolar mania, akathisia has been reported.^{10,62} At this time, the data are too limited to draw definitive conclusions regarding the EPS profile of aripiprazole.

Meta-analyses suggest that the most common adverse events (prevalence $\geq 10\%$ and $\geq$ placebo) associated with aripiprazole include headache, anxiety, insomnia, nausea, vomiting, light-headedness, somnolence, constipation, and akathisia.⁶⁰ In short-term trials, aripiprazole was associated with a 15% incidence of akathisia (compared with 4% with placebo) in patients with bipolar mania and a 0.71-kg increase in weight (compared with a 0.05-kg decrease with placebo) in patients with schizophrenia.^{10,60}

DISCUSSION

Antipsychotics are prescribed for a wide range of conditions. In addition to being the standard of care for psychosis, atypical antipsychotics are prescribed more than 70% of the time outside the FDA-approved labeling for patients with nonpsychotic conditions (e.g., anxiety disorder and mood stability in bipolar disorder).⁶⁷ Because primary care physicians are likely to prescribe an antipsychotic or see patients receiving these medications, it is important that they are aware of the differences that exist among the various atypical antipsychotics.

The main reason for the development of atypical antipsychotics was to provide an antipsychotic treatment option that was free of EPS and, further, to reduce the risk of tardive dyskinesia. Although many agents now claim to be atypical, the data presented suggest that only clozapine and quetiapine are true atypical antipsychotics. Of the available agents, clozapine and quetiapine show the lowest affinity for and the most rapid release from D₂ receptors.³ As a result, clozapine and quetiapine have been shown to have an incidence of EPS that was no different from placebo across the full dosage range.⁴

Promotion of risperidone, olanzapine, ziprasidone, and possibly aripiprazole has emphasized the atypicality of these agents; however, based on the data presented here, one should question whether these agents are truly atypical antipsychotics. Both risperidone and olanzapine have demonstrated EPS levels similar to placebo at low doses; at higher doses, however, EPS incidence for both agents becomes greater than with placebo.⁴ Data for ziprasidone are limited; however, ziprasidone appears to have an EPS risk similar to that of risperidone and olanzapine.^{56,57} Aripiprazole has been associated with akathisia; however, further study and experience with this drug are needed before definitive conclusions can be drawn.

CONCLUSION

A review of the pharmacologic and clinical information to date for all available antipsychotics would indicate that quetiapine and clozapine are the only "true" atypicals when one considers D₂-receptor activity, propensity toward EPS, and, by correlation, risk for tardive dyskinesia. Other agents cannot be considered atypical by this defini-

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tion, particularly if used in doses that cause EPS in general or akathisia in particular. Clinicians must consider the true definition of "atypical antipsychotic" when prescribing a newer agent and must ultimately be satisfied with the short-term and long-term safety of that agent.

Drug names: aripiprazole (Abilify), clozapine (Clozaril, FazaClo, and others), haloperidol (Haldol and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), ziprasidone (Geodon).

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ANEXO 3

Neuropharmacological profile of bifeprunox: Merits and limitations in comparison with other third-generation antipsychotics

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Schizophrenia is characterized by a range of positive and negative symptoms, and cognitive deficits. While positive symptoms respond to current antipsychotic agents, negative symptoms and cognitive deficits are often resistant to pharmacopeia. Thus research is now focused on developing third-generation antipsychotics that combine antagonism or partial agonism at dopamine D₂-like receptors with agonism at serotonin 5-HT_{1A} receptors. Such an association is anticipated to provide therapeutic benefits against a broader range of schizophrenia symptoms. Bifeprunox is one such third-generation antipsychotic agent which acts as a partial agonist at D₂-like receptors and is an efficacious agonist at 5-HT_{1A} receptors, with little interaction at 5-HT_{2A/C}, muscarinic or histaminergic H₁ receptors. This review summarizes the pharmacological profiles of the current antipsychotic agents and describes the rationale behind the development of third-generation antipsychotics. It also evaluates current data concerning bifeprunox in comparison with currently available antipsychotics, as well as those that are still under clinical development.

Keywords 5-HT_{1A} receptor, antipsychotic, bifeprunox, D₂-like receptor, schizophrenia

Introduction

Overview of schizophrenia

Schizophrenia, characterized by late adolescent or early adult onset and, in the majority of cases, a chronic course, is a devastating psychiatric disease with a lifetime prevalence of 1 to 5% [1]. This pathology presents multiple facets to overcome, including the overt positive symptoms (eg, hallucinations and delusions), negative symptoms (eg, flat affect, avolition and anergia) and cognitive dysfunction (eg, working memory [WM] impairment, perseveration and attention deficits). These cognitive deficits are considered part of the core symptoms of the pathology, and the limited efficacy of antipsychotics to control them hampers the social rehabilitation of patients [2,3]. In addition, approximately one third of patients are resistant to pharmacological treatment, underlining the need for more efficacious antipsychotic agents.

In vitro profile of current antipsychotic agents

All current antipsychotic agents interact, with varying potencies and selectivities, at dopamine (DA) D₂-like receptors, a property considered fundamental in the therapeutic mechanism of this class of agents. The presence

of dysfunctional dopaminergic neurotransmission in schizophrenia is supported by multiple observations, including PET studies showing that patients have an increased sensitivity to acute challenge with the DA releaser *d*-amphetamine [4], the abuse of DA-releasing amphetamine-like drugs producing psychotic episodes [5], antipsychotic compounds increasing the turnover of DA in the brain as a consequence of a blockade of DA receptors [6], and the correlation between the potency of antipsychotics used in the clinic for the control of psychosis and their *in vitro* affinity for the D₂ receptor subtype [7].

The first-generation antipsychotics (eg, chlorpromazine [Largactil] and haloperidol [Haldol]) potently antagonize D₂-like receptors and are thought to mediate their activity against the positive symptoms of schizophrenia by opposing the excessive stimulation of D₂-like receptors resulting from an overactivity of mesolimbic dopaminergic projections. However, these antipsychotics fail to alleviate the hypoactivity of mesocortical dopaminergic neurons, which is thought to underlie the negative symptoms and cognitive deficits [8]. In addition, selective D₂-like receptor antagonists also block nigrostriatal dopaminergic activity leading to extrapyramidal symptoms (EPS), including dystonia and dyskinesia. Furthermore, the blockade of pituitary-located D₂ receptors prevents tonic inhibition of prolactin release by endogenous DA, resulting in elevated plasma prolactin levels [9]. These observations have motivated the search for improved antipsychotics to not only control the positive symptoms of schizophrenia but also the negative symptoms and cognitive deficits, and with a diminished impact on EPS and prolactin.

In response to this need, the atypical (second-generation) antipsychotics were developed, including clozapine (Clozaril), risperidone (Risperdal), olanzapine (Zyprexa) and ziprasidone (Geodon; all Table 1). Clozapine partially fulfilled the improved therapeutic profile required through its actions at a variety of receptors other than D₂. It also acts as an antagonist at the D₄, D₁-like, 5-HT_{2A/2B/2C}, 5-HT_{6/7}, α_{1/2} adrenergic receptors, a muscarinic receptor antagonist (M1, M2, M3 and M5) or partial agonist (M4), and as a 5-HT_{1A} receptor partial agonist [10]. Furthermore, its principal metabolite, *N*-desmethylclozapine, is a partial agonist at D₂ receptors and the M1 to M5 receptors [11,12]. However, clozapine also potently antagonizes H₁ receptors, a property that likely underlies the sedation and metabolic disturbances observed with this antipsychotic agent. In addition, clozapine provokes potentially fatal agranulocytosis that prevents its use as a first-line treatment. The 'rich' (or 'dirty') pharmacological profile of clozapine has raised the issue of identifying compounds that exhibit combinations of receptor activities or 'pharmacological cocktails' that would yield an atypical profile without the metabolic/sedative side-effects. Risperidone is the most widely prescribed atypical antipsychotic agent and possesses more potent antagonist

Table 1. The structures and development status of antipsychotic agents possessing combined 5-HT_{1A} receptor agonism and D₂-like antagonism/partial agonism.

Compound	Structure	Development status
Aripiprazole (Otsuka Pharmaceutical Co Ltd/Bristol-Myers Squibb Co)		Launched
Clozapine (Novartis AG)		Launched
Olanzapine (Eli Lilly & Co)		Launched
Risperidone (Janssen Pharmaceutica NV)		Launched
Ziprasidone (Pfizer Inc)		Launched
Bifeprunox (Solvay SA/H Lundbeck AS/Wyeth Pharmaceuticals)		Pre-registration
RGH-188 (Gedeon Richter Ltd/Forest Laboratories Inc/Mitsubishi Pharma Corp)		Phase II
SLV-313 (Solvay SA/Wyeth Pharmaceuticals)		Phase I

Table 1. The structures and development status of antipsychotic agents possessing combined 5-HT_{1A} receptor agonism and D₂-like antagonism/partial agonism (continued).

Compound	Structure	Development status
F-15063 (Centre de Recherche Pierre Fabre)		Discovery
SSR-181507 (sanofi-aventis)		No development reported

properties at serotonin 5-HT_{2A} than D₂-like receptors [13]. Antagonism at 5-HT_{2A} receptors is also a key element of several other second-generation antipsychotics, including olanzapine and ziprasidone and is thought to contribute to their atypical profile by favoring dopaminergic neurotransmission in the frontal cortex, thus alleviating hypofrontality in schizophrenic patients [14,15]. However, these antipsychotics also exhibit shortcomings, including dose-dependent EPS (risperidone), metabolic disturbances (clozapine and olanzapine) and potential cardiac arrhythmia (ziprasidone) underlining the need for novel therapeutic approaches to the treatment of schizophrenia. Among the strategies developed to overcome these shortfalls [16], two have gained prominence in the identification of new third-generation antipsychotics with improved therapeutic activity and decreased incidence of side-effects. These increasingly utilized strategies include the selection of ligands with D₂-like receptor partial agonist properties as well as the selection of ligands with affinity for D₂-like receptors and agonist activity at 5-HT_{1A} receptors.

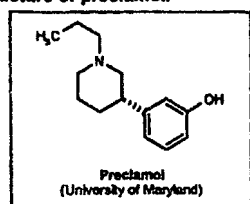
Rationale for the use of D₂-like receptor partial agonists in the treatment of schizophrenia

Several considerations, which are linked to improved tolerance and a potential efficacy for the treatment of psychosis, suggest that D₂-like receptor partial agonists (the 'DA stabilizers') could constitute successful therapies for schizophrenia; the premise being that partial agonists should be capable of opposing the excessive activation of receptors while maintaining a modest stimulation of the target sites. Thus, the benefits of conventional D₂-like receptor antagonism may be achieved (ie, their potential to reduce positive symptoms) without the side-effects induced by total blockade of these receptors. EPS are associated with antagonism of striatal D₂ receptors, and PET studies in humans with first-generation antipsychotics indicated that these symptoms are associated with high levels of occupancy (above ~ 70%), thus preventing normal signaling by endogenous DA [17]. In addition, a number of conventional antipsychotics exhibit inverse agonist properties at D₂ receptors *in vitro*, lowering the constitutive activation of the receptor [18,19]; however, such activity has not been demonstrated *in vivo*. In comparison, partial

agonists are an attractive option because they do not completely block D₂ receptor signaling, but rather stimulate a modest level of receptor activation even when high levels of receptor occupation are achieved, therefore reducing the likelihood of EPS. A further beneficial effect that could be achieved with the use of DA stabilizers relates to the antagonism of D₂ receptors expressed on pituitary-located lactotrophs, which prevents feedback inhibition of prolactin release by endogenous DA. As a result, D₂ receptor antagonists increase plasma prolactin levels, a response that can result in side-effects, including galactorrhea, gynecomastia and a negative impact on sexual functions [9]. Some of these side-effects can be attenuated by treatment with D₂ receptor agonists such as bromocriptine and cabergoline [20]. Therefore, a partial agonist at D₂ receptors would avoid the complete blockade of pituitary D₂ receptors and thus permit continued suppression of prolactin release, thereby reducing neuroendocrine disturbance. A further benefit could result from the fact that low doses of D₂-like receptor partial agonists preferentially activate presynaptic receptors, which control the synthesis and release of DA, as well as the firing rate of dopaminergic neurons [21•]. Thus, by activating presynaptic D₂-like receptors, partial agonists are predicted to attenuate over active mesolimbic DA neurotransmission, thus contributing to an antipsychotic action. As a complementary mechanism, partial agonism at overactive postsynaptic D₂-like receptors attenuates the activation induced by the endogenous full agonist (ie, DA), thus reinforcing the antipsychotic influence of the compound.

While the rationale for the use of partial agonists is attractive, the degree of D₂-like receptor partial agonism required to produce the proposed benefits is unclear. Several clinical studies with selective D₂-like receptor partial agonists, including talipexole, preclamol (University of Maryland; Figure 1), roxindole and pramipexole, failed to show a clear therapeutic effect on the positive symptoms of schizophrenia, although beneficial activity against negative symptoms has been suggested [22•]. Furthermore, the use of higher doses of partial agonists is associated with a worsening of positive symptoms, possibly related to the activation of postsynaptic D₂-like receptors [22•]. In one

Figure 1. The structure of preclamol.



early clinical study using preclamol there was a lack of a robust antipsychotic action and although significant antipsychotic effects were observed following one week of treatment, no effect was observed at the end of the second or third weeks, suggesting some adaptation or tolerance to the treatment [23]. As a result, a lower level of efficacy at D_2 -like receptors was suggested to be necessary to maintain antipsychotic response.

→ Aripiprazole (Abilify; Table 1) is the only antipsychotic agent with partial agonism at D_2 -like receptors that has achieved marketing approval [24]. In clinical trials, aripiprazole exhibited antipsychotic activity similar to that of haloperidol and risperidone [25]. The side-effect profile of this compound appears to be acceptable [25], although recent case studies suggest that it is not completely free from motor dysfunction liability, including tardive dyskinesia [26] and exacerbation of Parkinson's disease-related akinesia [27]. While the actions of aripiprazole at multiple receptor targets cannot be discounted [28], the partial agonist activity at D_2 -like receptors undoubtedly contributes significantly to its profile. However, the pharmacological relevance of aripiprazole's partial agonist properties is complicated by the fact that some of its metabolites exhibit antagonist activity in rats, which may oppose its partial agonist influence [29,30]. Thus, the rationale for the use of D_2 -like receptor partial agonists warrants further experimental and clinical validation with other D_2 -like partial agonists.

Rationale for associating 5-HT_{1A} receptor activation with D_2 -like receptor interaction

Compelling reasons exist to combine 5-HT_{1A} agonism with D_2 -like receptor interaction to form third-generation antipsychotic agents [31, 32,33,34]. Agonist activity at 5-HT_{1A} receptors may improve cognitive performance in patients with schizophrenia, including WM and reference memory (RM), and cognitive flexibility. 5-HT_{1A} receptors are upregulated in the frontal cortex of patients with schizophrenia, possibly as a compensation to insufficient activation of this site [35,36], and exploratory clinical trials have shown that 5-HT_{1A} receptor partial agonists do not impair [37] but rather ameliorate cognition in neuroleptic-treated patients with schizophrenia [38,39]. Furthermore, 5-HT_{1A} receptors are expressed on glutamatergic neurons in the frontal cortex where they decrease glutamate release in response to 5-HT_{1A} agonists [40]. This decrease influences signaling at glutamatergic receptors, including both NMDA and non-NMDA (ie, AMPA, kainate and metabotropic) receptors and might thus be involved in attenuating the cognitive and behavioral deficits induced by NMDA

receptor hypofunction. NMDA receptor blockade elicits excessive glutamate outflow which may contribute to mnesic/cognitive disruption in schizophrenia [41,42]. However, the neurocircuitry underlying the influence of 5-HT_{1A} receptors on cognitive function is complex, and the localization of this receptor has been demonstrated in several areas associated with the control of mood and cognition, including the hippocampus, lateral septum and entorhinal cortex [32,33]. Another reason to combine 5-HT_{1A} agonism with D_2 -like receptor interaction is that the activation of 5-HT_{1A} receptors may provide improved control of negative symptoms, including deficits in social interaction and mood. 5-HT_{1A} receptors are expressed in brain regions controlling frontal cortex dopaminergic neurotransmission, which is thought to influence negative symptomatology [33,43,44]. In microdialysis experiments, 5-HT_{1A} receptor agonists increased extracellular levels of DA in the frontal cortex [45-48], suggesting that they may alleviate hypofrontality in patients with schizophrenia. Furthermore, 5-HT_{1A} receptor partial agonists (eg, buspirone and tandospirone) are clinically effective in the treatment of generalized anxiety, which suggests that antipsychotics acting as 5-HT_{1A} agonists provide an additional beneficial influence on co-morbid mood disorders [34,49-51]. Further compelling reasons for developing a compound with combined 5-HT_{1A} agonism and D_2 -like receptor interaction include the observations that activation of 5-HT_{1A} receptors reduces EPS liability, and 5-HT_{1A} receptor agonists attenuate catalepsy induced by typical antipsychotics in rats [52-54] and EPS-related signs in non-human primates [55,56]. These findings indicate that 5-HT_{1A} activation should reduce EPS induced by D_2 receptor blockade. Clinical data to support this observation have been shown in add-on studies using buspirone or tandospirone, whereby EPS were attenuated in neuroleptic-treated patients with schizophrenia [57-60]. Finally, clozapine, ziprasidone and aripiprazole behave as partial agonists at 5-HT_{1A} receptors in various *in vitro* functional models [61-63]. 5-HT_{1A} receptor partial agonism underlies the anxiolytic and anticataleptic influence of clozapine in rats [64,65], suggesting that it may therefore contribute to clozapine's superior therapeutic profile. Based on the above rationale, several compounds with combined D_2 /5-HT_{1A} properties have also been investigated with varying success (see Table 1), including bifeprunox (DU-127090; Solvay SA/H Lunbeck AS/Wyeth Pharmaceuticals), SLV-313 (Solvay SA/Wyeth Pharmaceuticals) [66,67], RGH-188 (Cedeon Richter Ltd/Forest Laboratories Inc/Mitsubishi Pharma Corp) [68], SSR-181507 (sanofi-aventis) [69,70] and F-15063 (Centre de Recherche Pierre Fabre) [71-73].

Pharmacological profile of bifeprunox, a third-generation antipsychotic

Bifeprunox is the most advanced compound in development that fulfils the criteria for a third-generation antipsychotic. It selectively targets receptors of the D_2 -like family (D_2 , D_3 and D_4 receptors) and 5-HT_{1A} receptors, acting as a partial agonist at both targets (Table 2; [66,74]).

In two phase III clinical trials, bifeprunox (20 and 30 mg) displayed modest antipsychotic activity in patients with acute

psychosis, but the improvement was less marked than that observed with risperidone (6 mg), and an 8-day dose titration period was necessary in bifeprunox-treated patients to minimize adverse effects such as nausea and vomiting [75,76]. A third clinical study of acutely psychotic patients did not yield any significant effects following the administration of bifeprunox (20 and 30 mg), whereas olanzapine (15 mg) produced significant effects [77]. However, in all of these studies bifeprunox exhibited a favorable tolerance profile with minimal EPS and none of the metabolic interference associated with other antipsychotics, such as olanzapine. Bifeprunox reduced non-fasting cholesterol, glucose and triglyceride levels, and caused a slight decrease in body weight [75,76,77]. A long-term efficacy and safety study showed that bifeprunox (20 and 30 mg) was well tolerated over a 6-month treatment period and reduced the rate of psychopathological deterioration in patients with schizophrenia [78]. Studies examining the use of bifeprunox in patients with schizophrenia who have experienced side effects with current antipsychotics have not yet been reported but would be of considerable interest.

In vitro receptor profile of bifeprunox: Binding affinity

Original data for bifeprunox indicated pK_i values of 8.5 and 8.2 at human D₂ and 5-HT_{1A} receptors, respectively (Table 2) [79•]. However, methodological information is lacking and another study reported a wider separation (> 40-fold) in binding affinity between the two receptors, with a pK_i value of 7.2 at 5-HT_{1A} receptors in the rat cortex [62]. This reflects the fact that 5-HT_{1A} receptor actions of bifeprunox are principally observed at higher concentrations in measures of signal transduction *in vitro*, and in neurochemical measures of serotonin and DA release *in vivo* (see below). In comparison with other D₂-like receptors, bifeprunox has a high affinity at human D₃ and D₄ receptors, although discrepancy exists between the data reported for D₄ affinity by Marquis and

colleagues [79•] and those reported by other researchers (Table 2) [80]. While this issue requires further clarification, it is of interest to compare the difference in affinity for D₄ receptors between bifeprunox and aripiprazole.

It is significant to note that bifeprunox displays a weak interaction at 5-HT_{2A} and 5-HT_{2C} receptors, as this marks a departure from the 'recipe' that has guided antipsychotic drug discovery for the past two decades - that atypicality requires potent antagonism of 5-HT_{2A} receptors and more modest antagonism of D₂-like receptors [33]. Antipsychotics with this profile include clozapine, risperidone, olanzapine and ziprasidone, and while acting as a D₂ receptor partial agonist aripiprazole also exhibits antagonism of 5-HT_{2A} receptors (Table 2) [28]. Therefore, bifeprunox is the first antipsychotic to specifically target D₂-like and 5-HT_{1A} receptor activity, a fundamental property in the development of new third-generation antipsychotics. However, defining a generation of antipsychotics purely on *in vitro* binding data risks overlooking important information derived from functional studies. Even a relatively modest affinity at certain receptors could translate to marked physiological effects *in vivo*, depending on the level of agonist efficacy. In this context, it is interesting to note that although bifeprunox has a pK_i value at 5-HT₇ receptors of only 6.6 (Table 2) [81], it is the only antipsychotic to act as a partial agonist at this target (see below). Furthermore, the affinity of bifeprunox at 5-HT₇ receptors is similar to that of 8-OH-DPAT, a compound that has demonstrated influence at this receptor *in vivo* [82,83].

In addition, bifeprunox has a low affinity at a multitude of other receptors, including α₁ and α₂ adrenoceptors, and M1 and H₁ receptors, all of which are associated with various adverse effects. For example, potent α₁ antagonism is associated with orthostatic hypotension, and muscarinic

Table 2. *In vitro* binding profile of bifeprunox in comparison with aripiprazole.

Receptor	Radioligand	Tissue	pK _i values		Reference
			Bifeprunox	Aripiprazole	
h D ₂	NR	NR	8.5	8.3	[79•]
r D ₂	[³ H]nemonapride	Striatal membrane (r)	8.8	8.6	[62]
h D ₃	NR	NR	9.1	8.4	[79•]
h D ₄	NR	NR	8.0	7.0	[79•]
h D _{4.4}	[³ H]spiperone	CHO cell membrane	9.5	7.3	[80]
h 5-HT _{1A}	NR	NR	8.2	8.1	[79•]
r 5-HT _{1A}	[³ H]8-OH-DPAT	Cortex membrane (r)	7.2	7.4	[62]
h 5-HT _{1A}	[³ H]8-OH-DPAT	HeLa cell membrane	7.7	7.3	[62]
h 5-HT _{2A}	NR	NR	6.1	7.8	[79•]
h 5-HT _{2C}	NR	NR	< 6.0	7.3	[79•]
h 5-HT _{7A}	[³ H]5-CT	HEK293 cell membrane	6.6	6.7	[81]
r α ₁	NR	NR	6.9	7.0	[79•]
r α ₂	NR	NR	< 6.0	< 6.0	[79•]
h M1	NR	NR	< 6.0	< 6.0	[79•]
r H ₁	NR	NR	< 6.0	7.0	[79•]

h human, NR not reported, r rat.

receptor antagonism leads to autonomic side-effects such as dry mouth, constipation, and also possibly memory and cognitive disturbances [84]. Furthermore, blockade of H_1 and $5-HT_2C$ receptors may be responsible for problems of sedation and weight gain/metabolic disturbance observed with clozapine and olanzapine [84]. These *in vitro* data are consistent with the favorable tolerance profile of bifeprunox observed in clinical trials.

***In vitro* receptor profile of bifeprunox: Activation of signal transduction**

Multiple *in vitro* models have characterized the partial agonist properties of bifeprunox at D_2 -like receptors, including G-protein activation ($[^{35}S]$ GTP γ S binding), adenylyl cyclase inhibition (cAMP accumulation measures), ERK1/2 phosphorylation and G-protein-regulated inwardly rectifying K^+ (GIRK) channel currents in *Xenopus* oocytes (Table 3). In all of these measures bifeprunox behaves as a partial agonist at D_2 receptors, although E_{max} values differed between 26 and 76% depending on the experimental conditions and the reference ligand chosen as the full agonist comparator (Table 3). This raises an important question concerning the desirable level of agonist efficacy, because *in vitro* tests provide relative measures that do not necessarily reflect the agonist and/or antagonist properties displayed in humans. Therefore, other factors could modify the level of activation in different brain regions *in vivo*, including receptor expression levels, different G-protein subtypes and the presence of receptor dimers. In addition, it remains to be determined whether bifeprunox exhibits 'functional selectivity' (or agonist-directed trafficking of receptor signaling) at D_2 receptors, as has been reported for aripiprazole [19,28,29,85,86]. According to this concept, agonists may be highly efficacious or potent for some signal transduction pathways, but weak at others, possibly

influencing the therapeutic and/or side-effect profiles of the compounds. Nonetheless, bifeprunox has exhibited classic partial agonist properties in rat striatal slices, with a slight inhibition of adenylyl cyclase activity, while low concentrations (3 nM) attenuated the marked inhibition induced by the efficacious agonist quinpirole [87].

Bifeprunox also acts as a partial agonist (E_{max} values = 31 to 74%) at $5-HT_{1A}$ receptors but with substantially lower potency than at D_2 receptors (pEC_{50} ~ 6.5 versus ~ 8, respectively, indicating ~ 30-fold potency separation; Table 3). Thus, bifeprunox exhibited substantial efficacy but only modest potency in tests of G-protein activation at rat hippocampal $5-HT_{1A}$ receptors as well as cloned human $5-HT_{1A}$ receptors in recombinant cell lines. Modest potency was also observed in models of human $5-HT_{1A}$ receptor-mediated adenylyl cyclase inhibition [62] as well as ERK1/2 phosphorylation [88•]. Interestingly, other third-generation antipsychotics exhibit more balanced activities at $5-HT_{1A}$ and D_2 receptors, for example, SLV-313, SSR-181507 and aripiprazole show reinforced $5-HT_{1A}$ receptor activation relative to D_2 receptor interaction (Table 3) [89]. These data strongly suggest that in comparison with other novel antipsychotics, the activation of $5-HT_{1A}$ receptors by bifeprunox is expected to be less prominent than its activation of D_2 receptors.

Bifeprunox behaves as a partial agonist at D_4 receptors and at $5-HT_7$ receptors (Table 3) [80,81]. While the therapeutic relevance of these actions is unclear, weak partial agonism (or even antagonism) at D_4 receptors has been suggested to be beneficial in rodent [90-92] and monkey [93] models of cognition and exploratory behavior. With regards to $5-HT_7$ receptors, antagonist properties at this receptor may be involved in the control of the positive symptoms of

Table 3. *In vitro* functional influence of bifeprunox in models of dopaminergic and serotonergic receptor activation.

Receptor	Tissue	Efficacy measure	*Efficacy (%)	Potency (pEC_{50})	Reference
h D_{25}	Sf9 cell membrane	G-protein activation	26	8.56	[124]
h D_{25}	CHO cell	Adenylyl cyclase inhibition	28 (vs quinpirole)	nd	[79•]
h D_{25}	CHO cell	ERK1/2 phosphorylation	76	7.40	[88•]
h D_{2L}	<i>Xenopus</i> oocyte	GIRK channel currents	35 (vs quinpirole)	nd	[19]
r D_2	Rat striatal slice	Adenylyl cyclase inhibition	66 (vs quinpirole)	nd	[79•]
h $D_{4.4}$	CHO cell	G-protein activation	18	8.12	[80]
h $D_{4.4}$	<i>Xenopus</i> oocyte	GIRK channel currents	27	nd	[80]
r $5-HT_{1A}$	Rat hippocampal membrane	G-protein activation	36	6.37	[62]
h $5-HT_{1A}$	HeLa cell membrane	G-protein activation	61	6.49	[62]
h $5-HT_{1A}$	HeLa cell	Adenylyl cyclase inhibition	31	nd	[62]
h $5-HT_{1A}$	CHO cell	Adenylyl cyclase inhibition	73 (vs 8-OH-DPAT)	nd	[79•]
h $5-HT_{1A}$	CHO cell	ERK1/2 phosphorylation	74	6.46	[88•]
h $5-HT_7$	HEK293 cell	Adenylyl cyclase activation	20	5.32	[81]

CHO Chinese hamster ovary, GIRK G-protein-regulated inwardly rectifying K^+ , h human, nd not determined, r rat. * E_{max} values are expressed as a percentage of the effect of dopamine (for the D_2 and D_4 receptors) or of serotonin (for the $5-HT_{1A}$ and $5-HT_7$ receptors) unless otherwise stated.

schizophrenia [94-96]. However, activation of 5-HT₇ receptors enhances memory formation and attenuates dizocilpine-induced amnesia [97,98]. Furthermore, 5-HT₇ gene knockout mice showed impairments in contextual learning [99], suggesting that the 5-HT₇ receptor agonism exhibited by bifeprunox may be relevant to its activity in models of cognitive deficits of schizophrenia.

Neurochemical measures and electrophysiology

Dahan and colleagues investigated the electrophysiological measures of bifeprunox and reported that the compound partially inhibits tonic ventral tegmental area (VTA) firing activity while completely suppressing burst firing of VTA dopaminergic neurons (ED₁₀₀ = 200 µg/kg iv; Table 4) [100]. This activity was blocked by prior administration of haloperidol. In addition, bifeprunox (100 µg/kg iv) partially reversed the inhibitory effects of apomorphine on basal firing rates, consistent with partial agonism at presynaptic D₂-like receptors. In comparison, aripiprazole also suppresses VTA burst firing, which is in agreement with its recent description as a 'phasic component buster' [101]. Nevertheless, aripiprazole has a less marked influence on basal firing rates (~ 30% inhibition for aripiprazole versus ~ 50% for bifeprunox) [100], suggesting that bifeprunox has a greater agonist activity at VTA-localized D₂-like receptors. Bifeprunox also inhibits the firing of dorsal Raphe nucleus (DRN) serotonergic neurons (ED₁₀₀ = 482 µg/kg iv), consistent with agonist properties at somatodendritic 5-HT_{1A} receptors and confirmed by the fact that its influence is blocked by the selective 5-HT_{1A} receptor antagonist, WAY-100635. Interestingly, the potency of bifeprunox for suppressing VTA neuron burst firing is only 2.5-fold greater than its potency for inhibiting the electrical activity of DRN neurons [100]. This demonstrates that in electrophysiological measures a balanced influence is observed between the D₂-like and 5-HT_{1A} receptor partial agonist properties of bifeprunox, and contrasts with the wider separation seen *in vitro* and in neurochemical measures *in vivo* (see below).

Two studies have investigated the neurochemical properties of bifeprunox. Van Kolschoten and colleagues reported that bifeprunox modestly decreased nucleus accumbens serotonin levels (~ 25% below control), although the statistical significance of this effect was not reported (Table 4) [102]. In contrast, bifeprunox clearly decreased serotonin levels (50% below basal) in the ventral hippocampus [43]. This decrease, consistent with agonist properties at inhibitory presynaptic 5-HT_{1A} receptors, was blocked by pre-administration of WAY-100635, but was only observed at doses that are markedly higher than those which influenced DA levels and that were active in various behavioral tests of antipsychotic-like activity (2.5 mg/kg ip compared with 0.03 mg/kg, respectively). Similarly, decreases in serotonin synthesis rate (as determined by measuring 5-hydroxytryptophan [5-HTP] levels in the striatum) were only observed at oral doses of 10 and 30 mg/kg [102], whereas the selective 5-HT_{1A} receptor agonist, 8-OH-DPAT reduced 5-HTP levels at intraperitoneal doses from 0.3 mg/kg. These neurochemical

data indicate that bifeprunox only has a modest potency at 5-HT_{1A} autoreceptors controlling serotonin release.

Bifeprunox diminishes extracellular DA levels in the nucleus accumbens at low doses (0.03 to 0.3 mg/kg ip) consistent with its presynaptic D₂-like receptor agonist activity [102]. In the frontal cortex bifeprunox fails to increase DA levels, and actually tends to decrease them in this region [43]. This profile is similar to that reported for aripiprazole under the same conditions [43], and is a characteristic neurochemical response to partial agonists at D₂-like receptors. While a decrease in DA in the nucleus accumbens may contribute to the control of the positive symptoms of schizophrenia, established atypical antipsychotics (eg, clozapine, risperidone and olanzapine) substantially increase DA transmission in the frontal cortex, a response associated with a beneficial influence on negative symptoms and cognitive deficits [44]. Other putative third-generation antipsychotics under evaluation, including SLV-313, F-15063 and SSR-181507, also increase DA levels in the frontal cortex [43,103]. Thus, these neurochemical data question the extent to which increases in frontal cortex DA neurotransmission are necessary to attenuate deficits in cognition and/or negative symptoms, such as those elicited by NMDA receptor antagonism (see below). If increased dopaminergic neurotransmission is important to reduce the hypofrontality observed in patients with schizophrenia, bifeprunox may be less effective on some measures of fronto-cortical activity than other third-generation antipsychotics. It appears that the 5-HT_{1A} agonist properties of bifeprunox are insufficient to over-ride the predominant inhibitory influence of its agonist properties at D₂-like receptors on cortical DA release. An interesting comparison can be made with SSR-181507; this compound also exhibits D₂-like receptor partial agonism, but has a more pronounced 5-HT_{1A} agonist activity. Correspondingly, SSR-181507 significantly increases DA release in the rat frontal cortex [43,69].

Activity of bifeprunox in behavioral models of positive symptoms of schizophrenia

Consistent with its partial agonist properties at D₂-like receptors, bifeprunox opposes behaviors induced in rodents through the activation of dopaminergic neurotransmission. Thus, bifeprunox is active in conventional rodent models predictive of antipsychotic-like activity, including methylphenidate-induced stereotyped behaviors, *d*-amphetamine- or ketamine-induced hyperlocomotion and conditioned avoidance responding (ED₅₀ = 0.03 to 1.9 mg/kg ip) [102, 104,105,106,107]. Bifeprunox also blocks apomorphine-induced climbing behavior or phencyclidine (PCP)-induced hyperactivity in mice [105,108]. In a rat model of apomorphine-induced deficit of prepulse inhibition (PPI) of the startle reflex, bifeprunox is active at low doses (minimal effective dose [MED] = 0.04 mg/kg ip), although the dose-response curve shows an inverted U-shape (see below) [109]. While these data are consistent with activity against psychotic symptoms in schizophrenia, some additional comments must be made. First, the test of methylphenidate-induced behaviors is a rigorous evaluation of DA

Table 4. Pharmacological activity of bifeprunox in rat electrophysiological and neurochemical tests.

Model	Response	Route	*Dose (mg/kg)	Reference
VTA dopamine neuron firing	Inhibits VTA neuron burst firing	iv	200 µg/kg (ED ₁₀₀)	[100•]
DRN serotonin neuron firing	Inhibits DRN neuron firing	iv	482 µg/kg (ED ₁₀₀)	[100•]
Striatal levodopa accumulation	Minor increase in DA synthesis	po	10 to 30	[102•]
Striatal 5-HTP accumulation	Decreased 5-HT synthesis	po	10 to 30	[102•]
Medial pre-frontal cortex dopamine release	Does not increase dopamine levels	ip	0.63 to 10	[43•]
Nucleus accumbens dopamine release	Decreases dopamine	ip	0.03 to 0.3	[102•]
Ventral hippocampus 5-HT release	Decreases 5-HT	ip	2.5 to 40	[43•]
Nucleus accumbens 5-HT release	Modestly decreases 5-HT levels	ip	0.1 to 3	[102•]

DA dopamine, DRN dorsal Raphe nucleus, 5-HTP 5-hydroxytryptophan, VTA ventral tegmental area. *Unless otherwise stated, data indicate ED₅₀ values or active range.

receptor antagonism [110] and only incisive D₂-like receptor antagonists, such as haloperidol, risperidone, SLV-313 and F-15063, are able to completely reverse (or normalize) all of the observed stereotypic behaviors [72,107]. In contrast, bifeprunox potently blocks methylphenidate-induced gnawing (ED₅₀ = 0.08 mg/kg ip) but requires 60-fold higher doses to reverse the other behaviors (eg, rearing and sniffing). This separation of doses is likely a consequence of its partial agonism at D₂-like receptors and suggests that bifeprunox may not be as effective as antipsychotics that possess pure D₂-like receptor antagonism in controlling psychosis in patients with substantial dopaminergic hyperactivity (see above for comments regarding clinical efficacy). Thus, the use of bifeprunox may be of greater interest in stabilized patients, particularly in view of its favorable tolerance profile. In addition, there is some discrepancy between the doses reported in preliminary reports by Hertel and colleagues [105•,106] in tests of amphetamine-induced hyperactivity and conditioned avoidance responding, and those reported by Bardin and colleagues [107•]. The reasons for this are unclear, but may be related to differences in methodology and/or route of administration (ip versus sc; see Table 5). Clarification of this issue awaits publication of full methodological information.

Activity of bifeprunox in behavioral models of negative and cognitive symptoms of schizophrenia

As discussed earlier, controlling positive symptomatology is not sufficient to enable patients with schizophrenia to return to normal social activity; therefore there remains an unmet need for relieving the negative symptoms and memory/cognitive deficits associated with the pathology and it is essential that preclinical tests characterize potential antipsychotics in these terms. Based on the hypothesis that glutamatergic (NMDA receptor) interference is involved in schizophrenia [111,112], bifeprunox was compared with several other antipsychotics in three models of negative symptoms and deficits of cognition/memory produced by the non-competitive antagonist of NMDA-glutamatergic receptors, PCP [73,113,114•,115]. These models evaluated social interaction between two adult rats, spatial memory using a hole-board apparatus, and a reversal learning task (RLT) using a two-lever food-reinforced operant schedule.

When a pair of unfamiliar adult rats are placed in an open field, they will interact socially (eg, sniffing, following and climbing over one another), and PCP (2.5 mg/kg sc) reduces this level of interaction. Bifeprunox (0.01 to 0.63 mg/kg ip) failed to produce notable effects in this model of social interaction compared with other third-generation antipsychotics (SSR-181507, F-15063 and aripiprazole), all of which significantly opposed the deleterious effects of PCP, suggesting that their balance of dopaminergic and serotonergic properties are more favorable [73,113,114•]. The activity of aripiprazole, SSR-181507 and F-15063 for reversing of PCP-induced social interaction deficits is blocked by WAY-100635 (a 5-HT_{1A} receptor antagonist). These data suggest that the level of 5-HT_{1A} receptor agonism of bifeprunox is insufficient to show a beneficial effect in this test. In the holeboard model, the efficiency of rats to retrieve food pellets in four out of sixteen holes in the floor of an arena serves to calculate spatial memory indices, including WM and RM. Bifeprunox (0.63 mg/kg ip), SSR-181507 (1.25 mg/kg ip), F-15063 (0.04 mg/kg ip), aripiprazole (0.16 mg/kg ip) and haloperidol (0.04 mg/kg ip) all partially opposed the PCP (2.5 mg/kg)-induced deficits of WM and RM [115,116]. However, SSR-181507 and F-15063 were the only compounds that did not show deleterious effects of their own. Furthermore, and contrary to bifeprunox, both compounds increased exploratory behavior under basal conditions, suggestive of disinhibitory/pro-exploratory activity. Clozapine (0.63 mg/kg ip) exerted a marked sedative influence and was inactive in all parameters recorded, whether under basal conditions or with PCP [73,115]. These data suggest that bifeprunox may have favorable activity on some memory parameters associated with blockade of NMDA receptors. Finally, abundant experimental data support the implication of the cholinergic system in schizophrenia [117], justifying investigation of its sensitivity to antipsychotics. As a result, bifeprunox was investigated in a model of short-term memory: the scopolamine-induced deficit of social recognition [73,115]. In this model an adult rat was first exposed to a juvenile and then re-exposed 30 min later, with the decrease in time spent interacting during the second exposure providing an index of memory. Treatment with scopolamine disrupted this social recognition, consistent with the induction of amnesia.

Table 5. Pharmacological activity of bifeprunox in behavioral models.

Model	Response	Route	*Dose (mg/kg)	Reference
Rat				
Methylphenidate-induced behavior	Blocks gnawing	ip	0.08	[107•]
	Normalizes behavior	ip	1.8	
	Blocks gnawing	po	0.08	[107•]
	Normalizes behavior	po	5.2	
Amphetamine hyperlocomotion	Blocks hyperlocomotion	ip	0.63	[107•]
		sc	0.005	[105•]
Ketamine hyperlocomotion	Blocks hyperlocomotion	ip	1.25	[107•]
Conditioned avoidance	Blocks behavior	ip	0.03	[105•]
		sc	0.25	
Apomorphine-induced PPI deficit	Attenuates deficit	ip	0.04 to 2.5	[109]
Turning in rats with unilateral 6-OHDA lesions	Induces contralateral rotations	sc	0.026	[102•]
PCP-induced social interaction impairment	Does not augment interaction	ip	0.01 to 0.63	[114•]
PCP-induced deficit in holeboard	Improves working and reference memory	ip	0.16	[115]
	Diminishes latency time to first visit	ip	0.16	
	Scopolamine-induced social recognition deficit	Does not reverse deficit	ip	
Foot-shock-induced ultrasonic vocalization	Decreases vocalization	sc	0.02 to 0.16	[119]
S-32504 (D ₃ /D ₂ agonist) drug discrimination	No significant generalization to S-32504 cue	ip	0.63 to 5	[118]
Mouse				
Occupancy of striatal D ₂ receptors	Inhibits radiotracer binding <i>in vivo</i>	ip	0.25 (ID ₅₀)	[128]
PCP-induced hyperlocomotion	Blocks hyperlocomotion	sc	0.0072	[105•]
Apomorphine stereotypy	Blocks climbing	ip	0.03	[108]
	Blocks sniffing	ip	0.11	
Pigeon				
Flesinoxan (5-HT _{1A} agonist) discrimination	Partial generalization to flesinoxan cue	po	3	[119]

6-OHDA 6-hydroxydopamine, PCP phencyclidine, PPI prepulse inhibition. *Unless otherwise stated, data indicate ED₅₀ values or active range.

Among the series of antipsychotics tested, only clozapine, olanzapine, F-15063 and SLV-313 were active in this model whereas bifeprunox, over a wide dose range (0.01 to 0.63 mg/kg ip), did not significantly reverse the deficit [73,115]. It must also be noted that aripiprazole and SSR-181507 did not show activity, suggesting that partial agonism at D₂ receptors prevents attenuation of scopolamine-induced deficit in this model.

These data indicate that bifeprunox does not have as favorable a profile of activity in models of PCP or scopolamine-induced memory deficits compared with clozapine or some other third-generation antipsychotics, and suggest that its activity at D₂-like and 5-HT_{1A} receptors is less suited than that of other compounds in these models of cognition. However, prudence should be exerted when attempting to extrapolate these data to the clinical setting. Although differences may be detected between compounds in pharmacological models, atypical antipsychotics often do not demonstrate the capacity to alleviate cognitive dysfunction in patients with schizophrenia (as discussed previously). Therefore, further exploration of the properties of bifeprunox in models of cognition/memory is necessary in a wider variety of behavioral tests.

Activity of bifeprunox in other behavioral models

In models of anxiety and/or depression in rats, bifeprunox (ED₅₀ = 0.04 mg/kg sc) potentially reduces fear-induced ultrasonic vocalization (USV), a result reminiscent of that observed with clozapine [64]. This effect is abolished by co-administration of low doses of either haloperidol (0.04 mg/kg sc) or WAY-100635 (0.16 mg/kg sc) [104,106], suggesting that the actions of bifeprunox are mediated by a combination of both D₂-like and 5-HT_{1A} receptor activation. Additionally, bifeprunox (0.1 mg/kg) is active in the differential reinforcement of low rate operant schedule, a model that is sensitive to antidepressant compounds [104]. Finally, recent data show that bifeprunox and clozapine, but not aripiprazole, exhibit potent effects in a model of anxiety/compulsive behavior (marble burying in mice) [LA Bruins Slot, L Bardin, R Depoortere, A Newman-Tancredi, unpublished data]. These observations suggest the potential activity of bifeprunox against some aspects of the comorbid, anxious-depressive states of schizophrenia, and may differentiate bifeprunox from aripiprazole.

In drug discrimination experiments in rats utilizing S-32504 (a selective and efficacious D₃ vs D₂ receptor agonist) as the discriminative training stimulus, bifeprunox dose-

independently attenuates the cue, but did not significantly substitute at the highest dose tested (40% at 5 mg/kg ip) [118]. These data are consistent with the partial agonist/antagonist influence of bifeprunox at D₂-like receptors *in vivo*. Similarly, in pigeons trained to discriminate the efficacious 5-HT_{1A} receptor agonist flesinoxan from vehicle, bifeprunox substitutes only at a substantial dose (70% at 10 mg/kg po), suggesting a modest potency at 5-HT_{1A} receptors. The substitution by bifeprunox is blocked by co-treatment with the 5-HT_{1A} receptor antagonist DU-125530 [119], which is consistent with the partial agonist activity of bifeprunox at 5-HT_{1A} receptors.

In rats with unilateral 6-hydroxydopamine lesions of the substantia nigra (a classic model of Parkinson's disease), bifeprunox potently induced robust contralateral rotation behavior (ED₅₀ of 0.026 mg/kg sc) and displayed a maximal effect approximately two thirds of that observed with apomorphine [120]. Interestingly in the same model, aripiprazole failed to elicit rotation behavior at doses up to 2.5 mg/kg, providing evidence that bifeprunox has greater agonist properties at hypersensitive postsynaptic striatal D₂-like receptors. These data also support the potential utility of bifeprunox in the treatment of psychosis in patients with Parkinson's disease.

Activity of bifeprunox in models predictive of side effects

The maximal dose of bifeprunox tested (40 mg/kg ip) does not produce catalepsy in rats; however, in the presence of WAY-100635 (0.63 mg/kg sc), catalepsy has been observed [121]. This finding illustrates that the 5-HT_{1A} receptor agonist activity of bifeprunox is protective against the deleterious effects of D₂ receptor blockade in the striatum, which is responsible for catalepsy. Interestingly, this 5-HT_{1A} receptor influence only appeared at high doses of bifeprunox ($\geq$ 2.5 mg/kg ip) suggesting that the absence of catalepsy observed at lower doses of bifeprunox may be due to its partial agonist properties at D₂ receptors. The ED₅₀ ratio for inhibition of conditioned avoidance response, a model of antipsychotic-like activity (0.03 mg/kg ip) and induction of catalepsy ($>$ 40 mg/kg ip), yields a favorable antipsychotic versus EPS therapeutic ratio ($>$ 1000). Similarly, high ED₅₀ ratios were obtained against *d*-amphetamine hyperlocomotion ($>$ 100) or methylphenidate-induced gnawing (500) [107*].

In mice, bifeprunox induces catalepsy at doses widely separated from those active in tests predictive of antipsychotic activity; for example, the ED₅₀ for induction of catalepsy is 170-fold higher than that for inhibition of apomorphine-induced climbing [108]. Similarly to observations in rats, the low cataleptogenic potential of bifeprunox is influenced by its 5-HT_{1A} agonism, as co-treatment with WAY-100635 (2.5 mg/kg sc) produced a $>$ 10-fold shift to the left of the dose-response curve for catalepsy.

Some bifeprunox-induced dystonia is observed in neuroleptic-sensitized Cebus monkeys [122,123], but overall preclinical data showing minimal catalepsy are consistent

with clinical observations that bifeprunox produces only a very low incidence of EPS in patients with schizophrenia (as discussed earlier).

In neuroendocrine measures in rats, bifeprunox only produces a minimal increase in plasma levels of prolactin, even when administered intraperitoneally at a dose of 40 mg/kg [124]. As a result, hyperprolactinemia arising from D₂ receptor antagonism is unlikely to develop and lead to further adverse effects (see above). Thus, the limited impact of bifeprunox on prolactinemia is another reflection of its partial agonist activity at D₂ receptors and favorable tolerance profile.

Bifeprunox produces an inverted U-shaped dose-response curve in the test of apomorphine-induced disruption of PPI of the startle reflex in rats [109], a response pattern that may reflect its balance of D₂-like and 5-HT_{1A} properties. The partial agonism of bifeprunox at D₂ receptors may predominate at low doses (ie, 0.063 to 2.5 mg/kg ip), thus reversing apomorphine-induced PPI deficits. However, at higher doses (10 and 40 mg/kg), the 5-HT_{1A} agonist activity of bifeprunox occurs and exerts a deleterious effect on basal PPI [125]. When tested alone, bifeprunox produced a substantial deficit of basal PPI (MED = 10 mg/kg ip). All of the other clinically utilized antipsychotics, including aripiprazole, do not impair basal PPI in rats [126]. It is noteworthy that patients with schizophrenia already display an innate deficit of PPI that is associated with impaired functional status [127], and further impairment of PPI may constitute a disadvantage for bifeprunox if high doses are administered.

Discussion and conclusions

Bifeprunox and other third-generation antipsychotics: Influence of D₂-like receptor partial agonism

The development of novel third-generation antipsychotics combining D₂-like receptor antagonist/partial agonist activity with 5-HT_{1A} receptor partial agonism has generated a series of innovative compounds, including bifeprunox, SLV-313, SSR-181507, RGH-188 and F-15063, all of which display distinct balances of affinity and activity at D₂-like and 5-HT_{1A} receptors. Preclinically, bifeprunox displays activity in a broad range of models of antipsychotic-like properties and, in phase III clinical trials, was well tolerated and free from the metabolic interference or cardiac dysfunction that have plagued other antipsychotics (eg, clozapine, olanzapine and ziprasidone). Bifeprunox does not induce notable EPS or provoke hyperprolactinemia, which is consistent with its partial agonism at D₂-like receptors. However, the level of efficacy that is optimal for therapeutic activity is unclear. The D₂-like receptor agonist properties of bifeprunox are substantial, as observed *in vitro* and in its neurochemical and electrophysiological effects on dopaminergic neurotransmission (Table 4). *In vivo*, bifeprunox reverses amphetamine-induced hyperlocomotion in rats and apomorphine-induced stereotypy in mice, but fails to completely block behaviors induced in rats by methylphenidate. It is probable that the D₂-like partial agonist activity of bifeprunox causes its reduced activity in

the latter model, compared with D₂-like antagonists such as haloperidol, risperidone and the third-generation compounds SLV-313 and F-15063. Too high a level of D₂-like receptor agonist efficacy may impair control of florid psychotic episodes arising from hyper-dopaminergic states. Similar to much of the pharmacological data, results from recent clinical studies [75,76-78] have only been reported as poster presentations and full publication to enable a wider critical analysis with other antipsychotics are anticipated. Nevertheless, preliminary information from these posters indicates that bifeprunox displayed reduced antipsychotic activity compared with risperidone and olanzapine, and marked drop-out rates due to lack of efficacy suggest that its D₂-like agonist properties may be too accentuated. The D₂-like receptor partial agonist properties of bifeprunox may also underlie a higher clinical incidence of nausea and vomiting, leading to the need for dose titration.

Bifeprunox and other third-generation antipsychotics: Influence of 5-HT_{1A} partial agonism

The degree of 5-HT_{1A} receptor agonism desirable for optimal D₂-like/5-HT_{1A} receptor balance remains under debate. The 5-HT_{1A} receptor activity of bifeprunox *in vitro* is generally modest and, in neurochemical tests *in vivo*, is expressed at doses that are markedly higher than those at which D₂-like receptor activity has been observed. However, the doses at which bifeprunox inhibits VTA and DRN neuron firing are not widely separated (Table 4), suggesting increased 5-HT_{1A} receptor activation in electrophysiological measures. In addition, the fear-induced USV test (Table 5) showed an involvement of bifeprunox's 5-HT_{1A} receptor agonism at low doses and it would be interesting to determine if signs of 5-HT_{1A} receptor activation are observed clinically at antipsychotic doses. This issue is relevant because the D₂-like/5-HT_{1A} receptor balance of bifeprunox differs from that observed for other antipsychotics, including aripiprazole, which exhibits multiple interactions with diverse receptors [28] and low efficacy at 5-HT_{1A} receptors [62]. Other potential third-generation antipsychotics also show marked differences from bifeprunox. For example, SLV-313 is a chemical analog of bifeprunox and exhibits antagonist activity at D₂ receptors but potent 5-HT_{1A} partial agonism, while SSR-181507 combines potent 5-HT_{1A} agonism with partial D₂ receptor agonism (Table 1). F-15063 is a potent D₂ antagonist and weak 5-HT_{1A} agonist, as well as a D₄ receptor partial agonist [71-73]. Therefore, while sharing the common feature of targeting both D₂-like and 5-HT_{1A} receptors, these putative third-generation antipsychotics are clearly distinguishable in their receptor activity, and are therefore likely to display differing therapeutic profiles.

Bifeprunox and other third-generation antipsychotics: Activity on cognitive deficits

Increased cortical dopaminergic neurotransmission is considered to be important in controlling the negative symptoms and cognitive deficits in schizophrenia patients. However, while clozapine, olanzapine, risperidone, F-15063 and SLV-313 increased prefrontal cortex DA levels in microdialysis experiments, bifeprunox did not (Table 6).

This observation suggests that bifeprunox may be less effective than other antipsychotics in attenuating deficits that arise from impaired cortical dopaminergic function. When compared with other putative third-generation antipsychotics (ie, SSR-181507, F-15063 and SLV-313), bifeprunox was weakly active in a series of models of cognitive function in rats based upon glutamatergic (PCP-induced deficits) or cholinergic (scopolamine-induced deficits) interference (Table 6). Therefore, the therapeutic efficacy of bifeprunox on cognitive symptom measures compared with that of existing and other novel antipsychotic agents which display differing profiles of D₂/5-HT_{1A} receptor interaction is still to be determined. In addition, further investigation into the effects of bifeprunox in preclinical studies would be desirable, as would information concerning measures of cognitive performance from clinical trials.

Bifeprunox and aripiprazole: Are these compounds sufficiently different?

A key issue likely to influence market penetration of bifeprunox is its degree of similarity with aripiprazole. At the pharmacological level, the two compounds may be distinguished in models of D₂ receptor activation. For example, the efficacy of bifeprunox for activation of ERK1/2 phosphorylation and of GIRK currents at D_{2L} receptors is higher than that of aripiprazole (Table 3) [19,88]; however, G-protein activation experiments did not distinguish between the two compounds [124]. Bifeprunox also exerts greater inhibition on VTA neuron electrical activity than aripiprazole [100], reflecting higher efficacy at D₂ autoreceptors. Furthermore, bifeprunox potently induced contralateral rotations in rats with unilateral 6-hydroxy-dopamine lesions (Table 5), whereas aripiprazole was not active in this model [102]. These considerations suggest that bifeprunox may display accentuated D₂-like agonist properties compared with aripiprazole. At the therapeutic level, both antipsychotics have favorable tolerance profiles, as they are free from metabolic or cardiac interference, and therefore their use may be preferred in similar patient populations, for example, patients with stabilized psychotic symptoms who experience pronounced side-effects due to treatment with other antipsychotics. The observation that bifeprunox, in comparison with aripiprazole, displayed marked activity in rodent models of anxiety is intriguing and although preliminary, may provide an effective method of differentiating these antipsychotics. At the commercial level, bifeprunox will be launched (pending agreement by regulatory authorities) at a time when patent protection on aripiprazole will have expired, underlining the further need to adequately distinguish the two compounds. Finally, and despite its limitations, it is clear that bifeprunox would benefit from a 'first in class' advantage as a selective D₂/5-HT_{1A} partial agonist antipsychotic and, together with its favorable tolerance profile, will generate interest from both a clinical and a drug discovery perspective.

Disclosure

The authors are employees of the Pierre Fabre Research Centre.

Table 6. Comparative pharmacological activity of third-generation antipsychotics.

Experimental model	Bifeprunox	Aripiprazole	SLV-313	SSR-18157	F-18063	Clozapine	Haloperidol	References
D ₂ binding affinity	++	+	++	+	++	+/0	++	[62,71]
D ₂ efficacy (partial agonism)	+	+	0	+	0	0	0	[19,71,88,124]
5-HT _{1A} binding affinity	+	+	++	++	+	+/0	0	[62,71]
5-HT _{1A} efficacy (agonism)	+	+	++	++	++	+	0	[62,71]
Antagonism of amphetamine, ketamine-induced hyperactivity in rats	++	+	++	+	++	+	++	[72,107•]
Antagonism of methylphenidate-induced behaviors	+	+	++	+	++	+	++	[72,107•]
Antagonism of apomorphine-induced stereotypy	++	+	++	+	++	+	++	[107•,108]
Inhibition of conditioned avoidance behavior	++	+	++	++	++	+	++	[72,107•]
Reversal of apomorphine-induced PPI deficit	+	0	0	0	+	+	++	[72,109]
Increased medial prefrontal cortex dopamine levels	0	0	+	+	+	++	+/0	[43•,103]
Reversal of scopolamine-induced social recognition deficit	0	0	+	0	++	+	0	[73,115]
Reversal of PCP-induced memory deficits: holeboard test	+	+	+	+	+	sedation	+	[115,116]
Reversal of PCP-induced social interaction deficits	0	++	0	+	+	0	0	[73,114•]
Induction of catalepsy	0	0	0	0	0	0	++	[72,107•,108,121]
Increased plasma prolactin levels	0	+/0	++	+/0	++	+	++	[88•]
Induction of memory deficits: holeboard test	+	+	0	0	0	sedation	+	[73,115]
Induction of PPI deficits	+	0	+/0	++	0	0	0	[128]
Decreased hippocampal serotonin levels	+	0	+	+	+	0	0	[43•,103]

0 no influence, +/0 weak influence, + marked effects, ++ very marked effects, PCP phencyclidine, PPI prepulse inhibition.

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