■表3 薬物動態に関する性差（最高血中濃度，AUC，CLおよび代謝物の生成などから評価）

薬物名	性差	関与する酵素	発表者
olanzapine	M>F	1A2, 2D6, UGT	Callaghan, J. T. (1999)
clozapine	M>F	1A2, 3A4	Lane, H. Y. (1999)
mephenytoin	F≒M	2C19	Hulstek (1994)；Laine, K. (2000)
	F>M	2C19	May, D. G. (1994)；Xie, H-G. (1997)；Xie, H-G. (2000)
	M>F	2C19	Tamminga, W. J. (1999)
mephobarbital	M>F	2C19	Hopper, W. D. (1990)
diazepam	F>M	2C19, 3A4	Greenblatt, D. J. (1980)；Ochs H. J. (1981)
chlorpromazine fluphenazine	M>F	2D6	Yon Kers, K. A. (1992)
triazolam	F≧M	3A4	Greenblatt, D. J. (2000)
nitrazepam	F≒M	3A4	Jochemsen, R. (1982)
bromazepam	F≒M	3A4	O'chs, H. J. (1981)
midazolam (iv) midazolam (po)	M≒F M>F	3A4	Thummel, K. E. (1996)；Kinirons, M. T. (1999)
midazolam (iv) midazolam (po)	M≒F M<F	3A4	Gorski, J. C. (1998)
midazolam (iv)	M≒F	3A4	Kashuba, A. D. (1998)
midazolam (po)	F>M	3A4	Tsumoda, S. M. (1999)
oxazepam	M>F	UGT1A	Greenblatt, D. J. (1980)；Wilson, K. (1984)
temazepam	M>F	UGT1A	Divoll, M. (1981)
olanzapine	M>F	UGT	Skogh, E. (2002)

投与経路が記載していないものは経口投与を示す。　加藤隆一：臨床薬物動態学改訂第3版, 2003より改変。

がある。

26種の薬剤を用いて性差を比較した研究[6]では，以下の結果が得られている。すなわち，体重補正後は15%の薬で男女間に有意差が認められ，そのすべてにおいて男性のほうが高い代謝活性を示した。個人内の変動は女性のほうが大きかった。

薬剤によっては性差が認められることもあるが，この差に比べてヒトにおける薬物動態の個人差は極めて大きいため，統計学的に有意差のある報告が少ないと考えられる。男女間の体重，脂肪量の差を考慮するとともに，今後のさらなる研究が性差の実態を明らかにするために必要とされるであろう。

(3) 食事・嗜好品

ヒトにおける薬物動態の個人差は，遺伝的因子とともに環境因子によるところが大きい。環境因子の中でも，特に喫煙，アルコール，コーヒーなどの嗜好品や食事の差に由来する因子が薬物動態の変動に影響を与える。

喫煙者では，非喫煙者に比し，fluvoxamineの血中濃度が有意に低下し[34]，これは喫煙によりCYP1A2が誘導されるためとされている。

同量のquazepamを投与した場合，血中濃度は食後に服用したほうが空腹時に服用するより有意に上昇することが知られている[41]。薬物の半減期には差がないことから，食事が薬物の吸収に影響を与えると考えられている。食事によって胆汁排泄が増加し胃液，腸液が増加することから，溶解性の低い薬物ほど食事によって吸収率が上昇する。Quazepamは溶解性が低いため，食事によって著明に吸収率が増加すると考えられる。

グレープフルーツジュースを服薬と同時に摂取することによりtriazolamなどの血中濃度が増加することが知られているが，これは肝のみでなく小腸にも高い活性を認めているCYP3A4が，グレープフルーツジュースによってその活性を阻害されるためと考えられている。

St. John's Wort（西洋オトギリソウ）はヨーロッパで薬草として伝統的に用いられてきたが，St. John's Wortからの抽出物であるLI160をamitriptylineと併用したところ，amitriptylineとその代謝物の血中濃度が有意に低下した[15]。これはCYP3A4やMDR1がSt. John's Wortによって誘導されるためと考えられている。

3. 人種差

以前は，一定の条件を満たす外国で実施された臨床試験データは承認審査資料として受け入れられてきたが，データの内容にかかわらず，吸収・分布・代謝・排泄に関する試験，投与量設定に関する試験および比較臨床試験等の国内臨床試験データの提出を求められてきた。しかし，1998年の日米EU医薬品規制調和国際会議（International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use：ICH）の指針を受け，厚生省（当時）より，医薬品等の製造（輸入）承認審査資料として，できるだけ外国で実施された臨床試験データを活用する旨の通知がなされた[19]。ICH指針では，医薬品の効果に影響する民族的要因を外因性・内因性の2種類に分類している（図1）。

これらの要因の中で最も主要な要因は，薬物動態（特に薬物代謝）の人種差である。分子生物学の進歩によって，薬物代謝の表現型・遺伝子多型に関する研究が急速に進められ，薬物代謝の表現型・遺伝子多型の分布は人種によって大きく異なることが知られるようになった。このような薬物代謝の人種差に関する情報は，異なる人種間のデータのやりとりを容易にするばかりでなく，新たな臨床試験を計画する上での参考になり，その結果の解釈を容易にし，予期せぬ副作用や相互作用を回避するなど，臨床試験に種々の恩恵をもたらすものと考えられる。

肝臓での薬物代謝において重要な役割を演じているのがCYPである。臨床現場で用いられている薬剤の80％以上がCYPによって代謝されるといわれている。特にCYP2D6とCYP2C19は多く

内因性民族的要因		外因性民族的要因
遺伝的要因	生理的・病理的要因	環境要因
性	年齢	気候
身長		日光
体重		環境汚染
	肝臓	
	腎臓	文化
	心・血管機能	社会経済的要因
吸収・分布・代謝・排泄		教育水準
レセプターの感受性		言語
人種		
薬物代謝の遺伝多型		医療習慣
遺伝病		疾病の定義・診断
		治療法
		服薬遵守の程度
	喫煙	
	飲酒	
	食事習慣	
	ストレス	
	疾患	規制方法
		臨床試験の実施方法／エンドポイント

■図1 内因性および外因性民族的要因の分類[19]

の向精神薬の代謝に関与する，精神科領域で重要な酵素である。以下に，CYP2D6とCYP2C19の人種差に関する報告を示す。

(1) CYP2D6

コーカソイドのCYP2D6 *3，CYP2D6 *4，CYP2D6 *5のアレル頻度はそれぞれ，0.02，0.22，0.04である[5]。東洋人の場合は，CYP2D6 *3，CYP2D6 *4，CYP2D6 *5のアレル頻度は，0，0.002，0.045であり[26]，これらのアレルをホモでもつ個体は非常に少ない。これらの変異遺伝子をホモでもつ個体は，CYP2D6代謝活性が欠損し，コーカソイドのpoor metabolizerの95%以上がCYP2D6 *3，CYP2D6 *4，CYP2D6 *5による変異遺伝子で説明される。また，これらの変異遺伝子を野生型遺伝子（CYP2D6 *1）とヘテロでもつ個体も，CYP2D6 *1をホモでもつ個体と比べて，CYP2D6代謝活性が低下する。

一方，東洋人は酵素活性の低下に関係するCYP2D6 *10のアレル頻度が野生型に次いで高く(0.381)，この変異遺伝子をホモでもつ個体，あるいは*10と*5をヘテロでもつ個体はCYP2D6代謝活性が低下する。また，*1と*10あるいは*2と*10をヘテロでもつ個体も，薬物によっては代謝活性の低下がみられる。これら変異遺伝子の分布の違いによって，薬物代謝の人種差の主要な部分が説明されると考えられる。

これまで東洋人では，CYP2D6のpoor metabolizerの頻度は1%以下であることから，CYP2D6の遺伝子多型はあまり重要視されなかったが，*10の遺伝子変異によっても薬物代謝活性が大きく異なることが明らかとなり，今後臨床試験における遺伝子型同定の重要性がますます高まるものと思われる。

また，*2アレルを複数個もつ個体は，代謝活性が増加する（ultrarapid metabolizer）ことによって基質となる薬物の血中濃度低下をきたすが，アレル頻度はコーカソイドで0.01～0.035，日本人では0.005～0.01と極めて少ない[26,28]。

(2) CYP2C19

CYP2C19のpoor metabolizerの頻度は，コーカソイドでは約3%であるのに対し，アジアーモンゴロイドでは10～20%と高く[5]，ジンバブエのネグロイドでは約4%である。また，同じextensive metabolizerに分類される群でも，アジアーモンゴロイドはコーカソイドより4'-水酸化活性が低いことが知られており，これは変異遺伝子をヘテロでもつ個体が多いためと考えられる。

CYP2C19 *2はさまざまな人種でみられるが，CYP2C19 *3はアジアーモンゴロイドで主にみられる。日本人のpoor metabolizerはこれら2つの変異遺伝子でほぼ100%説明できるが[8]，コーカソイドでは85%しか説明できない[9]。

まとめ

薬物代謝能は基本的な個人差が大きく，投与された薬物によってはその体内動態に著しい個人差が生じる。薬物動態の個人差による薬効の低下や有害事象の発現を避けるため，血漿薬物濃度を測定（therapeutic drug monitoring：TDM）することにより，個人に適した薬物，用量を投与する必要がある。同時に，薬物動態上大きな個人差が起こる可能性のある薬物の開発を避けることや，遺伝子多型の同定により薬効を得にくい人，有害事象が出現しやすい人をあらかじめ見いだしておくことが，今後の医療にとって重要となるであろう。

薬力学的な個人差については未知の部分が多く，現時点で臨床応用できる報告は少ない。薬力学的に薬効の低下や有害事象の発現の個人差に影響を与えている遺伝子多型の解明が切望されている。

（鈴木雄太郎，渡邉純蔵，染矢俊幸）

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Part 2 SSRIの臨床薬理

4．SSRIの薬物動態と代謝 —フルボキサミン，パロキセチンを中心に—

はじめに

わが国における抗うつ薬治療において，選択的セロトニン再取り込み阻害薬（selective serotonin reuptake inhibitor：SSRI）やセロトニン・ノルアドレナリン再取り込み阻害薬（serotonin noradrenaline reuptake inhibitor：SNRI）などが，従来の三環系抗うつ薬に代わり，第一選択薬として使用されるようになったことは今さらいうまでもない．SSRIは従来の三環系抗うつ薬にくらべて同等の臨床効果を有しながら，抗コリン作用や心毒性といった有害作用が少なく，安全性において高い評価を得ている．

一般に，同一薬剤，同一用量であっても個人間で薬物血中濃度に大きなばらつきがあることが知られている．臨床効果や副作用の出現などを用量のみで予測することは困難であり，薬物血中濃度モニタリング（therapeutic drug monitoring：TDM）を利用して治療計画を立てることが望まれているが，三環系抗うつ薬に関してはTDMに関する研究が蓄積され，その有用性が認められているのに対し，SSRIやSNRIに関してはTDMの有用性はまだ確立しておらず，臨床レベルで利用されるまでには至っていない．

また高齢者では種々の身体疾患を合併し多くの薬物を併用していることや，組織での薬物に対する感受性が高まっていることなどから，副作用の発現が多い．さらに肝疾患や腎疾患など種々の病態下における薬物の体内動態に著しい変化があることも知られている．臨床医は精神症状の改善や副作用を臨床的に評価するだけでなく，使用する薬剤についてさまざまな状況における体内薬物動態・代謝，他の薬剤との相互作用についても熟知しておく必要がある．

ここではフルボキサミンとパロキセチンを中心に，SSRIの薬物動態と代謝について概説する．

1．体内薬物動態・代謝

まずはじめに，本稿で概説する各種SSRIの体内薬物動態的パラメータ（表❶）[1]および主要な代謝酵素（表❷）[2]をそれぞれ示す．

1）フルボキサミン

①吸収・分布・代謝・排泄

経口投与されたフルボキサミンは，食事などの影響を受けずにそのほとんど（約94%）が消化管より吸収される．その後，肝臓で代謝され，

表❶ SSRIの体内薬物動態的パラメータ

	生体利用率 (%)	血漿蛋白結合性 (%)	分布容積 (L/kg)	クリアランス (L/h)	半減期 平均 (h)	半減期 範囲 (h)	定常状態の平均血中濃度(ng/mL)
フルボキサミン	>53	77	>5	80 (33～220)	15	9～28	20～500
パロキセチン	>64	93	17	36～167	18	7～65	10～600
セルトラリン	>44	98	25	96	26	22～36	20～200
fluoxetine	80	95	25	10～36	45	24～144	90～300

(DeVane CL, 1998[1]より改変引用)

表❷ SSRIの主要な代謝酵素

親化合物	主要な代謝産物	代謝酵素
フルボキサミン	特になし	CYP1 A2，CYP2D6
パロキセチン		CYP2D6
セルトラリン	desmethylsertraline	CYP2C9，CYP3 A4
fluoxetine		CYP2C9 (CYP3 A4，CYP2D6)

(Greenblatt DJ *et al*, 1998[2] より改変引用)

フルボキサミンのまま体循環に入る割合は約53%とされている[3]．フルボキサミン25，50，100 mgを健康成人に1回投与した場合の最高血清中濃度（Cmax）は，それぞれ9.17，18.0，38.1 ng/mLとほぼ直線的に増加し，最高血清中濃度到達時間（Tmax）は2～8時間（平均5時間）と報告されている．しかしフルボキサミン100，200，300 mgという高用量を10日間反復投与した結果，血中濃度がそれぞれ88，283，546 ng/mLと非直線的に増加したという報告もある[4]．

フルボキサミンは他の三環系抗うつ薬や抗精神病薬と同様に，血中よりも肺・肝・腎などの主要な臓器でより高い濃度を示すことが動物実験で示されている．このことはフルボキサミンの疎水性が高いためであり，透析患者などへのフルボキサミンの補充が必要でないことを意味している．フルボキサミンの分布容積は約5L/kgであり，特定の臓器への異常な蓄積性は認められていない[3]．

フルボキサミンの血漿蛋白結合性は約77%であり，すべてのSSRI中最も低いとされている．高蛋白結合性の薬物同士の併用は，非結合型の血中薬物濃度を上昇させるが，フルボキサミンにおいては蛋白結合を介した他の薬物との相互作用は比較的少ないと考えられる[3]．

^{14}C-ラベル体を用いたフルボキサミン経口投与試験によれば，投与後71時間までの尿中放射能総排泄率は平均94%であり[4]，このうちフルボキサミンの未変化体は4%以下であった[3]．半減期は約9～28時間であり[1]，投与量による影響はあまりないものと考えられている．仮に投与量を変更した場合，新たに定常状態に達するには約5日間が必要であると考えられる[5]．

わが国のフルボキサミン第Ⅰ相試験の結果では，25，50，100，200 mg単回投与におけるCmaxはそれぞれ9.14，17.25，43.77，91.81 ng/mL，Tmaxはそれぞれ5.17，4.67，3.50，4.67時間であり，75 mgの6日間反復投与では，3日間で定常状態（10.6 ng/mL）に達したと報告されている[6]．また4週間の投与試験においても蓄積性は認められず，平均100 mgの投与量の範囲では用量依存性に血中濃度が増加していた[7]．

フルボキサミンの代謝にはチトクロームP450 (CYP) 2D6および1A2が関与するとされ

ている（図❶-①）[8]．CYP1 A2の関与については，喫煙がCYP1 A2を誘導すること，フルボキサミン内服中の喫煙者においてはフルボキサミン血中濃度が非喫煙者にくらべて有意に低いことから説明されている[3)9)]．また，CYP2D6についてはデブリソキンやデキストロメトルファンを試験薬として用いた研究において，フルボキサミンの薬物動態にCYP2D6の関与を示唆した報告がある[10]．

②高齢者

フルボキサミン50，100 mgを65歳以上の高齢者に単回投与した場合，Cmaxが約40%上昇したという報告があり，同じ投与量で定常状態にある高齢者では，半減期が130～160%延長したとされている[11]．

わが国での高齢者（65歳以上）うつ病・うつ状態患者に対する臨床試験においても，平均の血中濃度が増加する傾向が認められている[12]．この試験ではより重篤な副作用は認められなかったものの，高齢者においてはより低用量からの慎重な薬剤投与が必要であると考えられる．

③肝機能・腎機能障害者

肝硬変などの肝機能障害を有する患者では肝におけるフルボキサミンのクリアランスが30%ほど減少することが示唆されていることから，血中濃度が上昇する可能性が予測され，肝機能障害の患者にフルボキサミンを投与する場合には低用量から開始すべきである．一方，血清アルブミンの減少がフルボキサミンの薬物動態に与える影響は比較的少ないとされている[3)4)]．

腎機能障害を有する患者においてはフルボキサミンの血中濃度が変化しないという報告があるが，フルボキサミンの代謝産物のほとんどが尿中に認められること，高度の腎機能障害が肝機能を低下させてしまうことなどを考慮して，腎機能障害を有する患者においても低用量からの投与が適当であろう[3]．

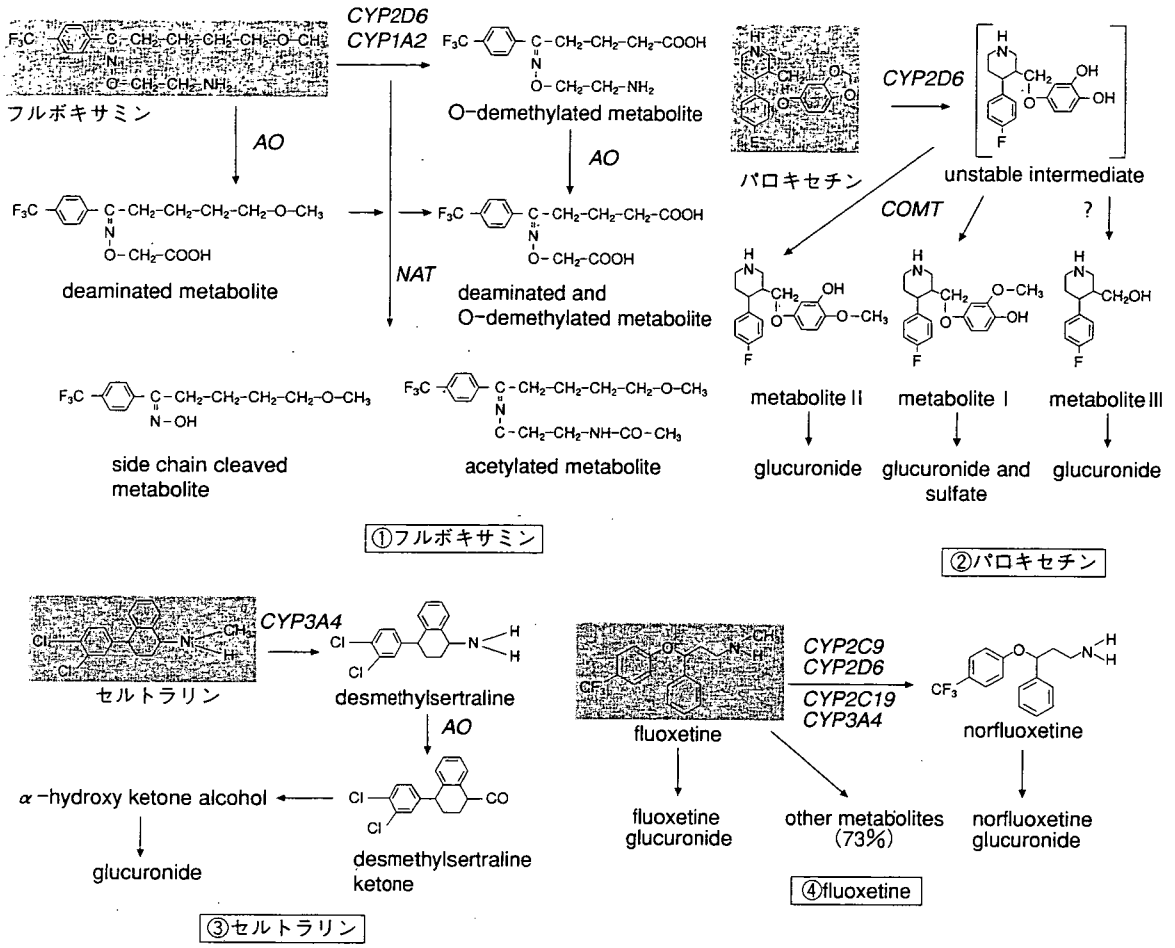
2）パロキセチン

①吸収・分布・代謝・排泄

^{14}C-ラベル体を用いたパロキセチンの健常成人への単回投与は，消化管からほぼ完全に吸収される[13]．パロキセチンの分布容積は3～12L/kgでありフルボキサミンの分布容積（5L/kg）にほぼ等しい[8]．またパロキセチンのヒト血漿蛋白結合性は血中濃度100，400 ng/mLでそれぞれ93，95%であり，フェニトイン，ワルファリンの血漿蛋白結合性に影響を与えないとされている[14]．

パロキセチンの代謝には少なくとも2つの経路が関与しており（図❶-②），一つはCYP2D6の関与する飽和型の代謝経路であり，もう一つはCYP2D6以外のCYPアイソエンザイムによる代謝経路である．パロキセチンでは薬物動態の非線形性が報告されているが，CYP2D6以外の代謝経路が別に存在していることもこのことに関連している[15]．また*CYP2D6*遺伝子の変異アレルおよびパロキセチンの用量が血中濃度に与える影響が報告されており，パロキセチンの血中濃度について変異アレルを有する群と有さない群とで比較した場合，低用量（10 mg/日）では変異アレルをもつ群で血中濃度が有意に高かったとされている[16]．

パロキセチン30 mgを30日間経口投与した場合，約10日間で定常状態に達し，平均Cmax，Tmax，Cmin（最低血清中濃度），半減期はそれぞれ61.7 ng/mL，5.2時間，30.7 ng/mL，21.0時間と報告されている[17]．CmaxおよびCminの値はパロキセチン単回投与の報告から予測される値にくらべて，それぞれ6倍，14倍と高い．前述したパロキセチン薬物動態の非線形性に関しては，投与量で補正した薬物血中濃度時間曲線下面積（area under the drug concentration time curve：AUC）比が，西欧人で0.8～7.6，日本人



図❶　各種 SSRI 代謝動態

(Hiemke C *et al*, 2000[8]より改変引用)

で 1.1～5.9 であり，1 をほとんど超えていること，健常成人（日本人）にパロキセチン 10, 20, および 40 mg を単回投与したときの Cmax および AUC は，投与量増加の割合を上回って増加していることなどからも示唆されている[13)15)]．このような非線形性を示す理由として，パロキセチンの代謝酵素 CYP2D6 の飽和または自己阻害（self inhibition）が関与していることが指摘されている[14)]．

パロキセチンは酸化，抱合を受けて代謝されるが，その代謝産物は薬理学的活性をほとんどもたない．30 mg を 10 日間経口投与されたパロキセチンの約 64%が尿中に（うち 2%が未変化体），約 36%が糞便中に（うち未変化体は 1%以下）認められている[18)]．

②高齢者

加齢による影響は，パロキセチンの薬物動態に大きな変化を与えることはなく，臨床的にも血圧や脈拍，臨床検査や心電図などで問題となる変化はみられないとする報告がある[19)20)]．しかし若年者と比較してパロキセチンの Cmin が 70～80%増加したという報告などもあり[14)]，パロキセチンにおいても高齢者への投与は低用量から慎重におこなうべきと考えられる．

③肝機能・腎機能障害者

わが国の研究においては，軽微な肝機能・腎機能障害患者に対するパロキセチンの薬物動態は健常者とくらべて有意な差は認められなかった[19]．しかしクレアチニン・クリアランスが30～60 mL/分の患者および肝機能障害の患者においてパロキセチンの血中濃度が約2倍，クレアチニン・クリアランス30 mL/分以下の患者では約4倍に上昇するという報告もある[14]．

3）その他のSSRI

①セルトラリン

セルトラリン単回投与によるわが国の第Ⅰ相試験では，投与後約6～9時間で最高血中濃度に達し，半減期は約23～24時間であり，1日1回投与が可能であることが示唆されている[21]．Cmax，AUCもほぼ用量依存的に増加し，100 mgの反復投与試験では4～7日で定常状態（40.4～43.9 ng/mL）に達した[22]．また薬物動態に関しては食事の影響を受けないとされている[23]．

経口投与されたセルトラリンはおもに肝臓で代謝される．この代謝にはCYP3 A4やCYP2C9が関連していることが示唆されており[24]（図❶-③），CYP2D6の関与は大きくないといわれている[25]．主要な代謝産物にN-desmethylsertralineがあり，この半減期は62～104時間，薬効はセルトラリンの1/10以下であると考えられている[26]．

放射性物質でラベルされたセルトラリンを経口投与した場合，投与後9日目までの尿中放射能総排泄率は40～45%であり，未変化体は認められない．糞便中への排泄率は40～45%であり，うち12～14%がセルトラリンの未変化体であった[27]．また，セルトラリンの血漿蛋白結合性は約98%と高く，他の蛋白結合性が高い薬物との相互作用に注意が必要である[28]．

高齢者では若年者と比較してセルトラリンのクリアランスが40%減少する．また高齢者うつ病患者（65歳以上）に対する臨床試験の結果では，若年者と比較して半減期が延長する傾向が認められた[29]．

肝機能障害患者においては半減期が延長し，Cmax，AUCも増加したという報告があるが，腎機能障害患者におけるセルトラリンの薬物動態は明らかでない[27]．

②fluoxetine

fluoxetineはR-fluoxetineとS-fluoxetineといった鏡像異性体を等分にもつ混合物であり，S体はR体にくらべて血中からの消失速度が遅いため，定常状態ではS体が優位である[30]．R,S-fluoxetineはそれぞれ肝臓で脱メチル化され，R,S-norfluoxetineに代謝される．R,S-fluoxetine，R,S-norfluoxetineともに同程度のセロトニン阻害作用を有するが，R-norfluoxetineはS-norfluoxetineの1/22の活性しか有さない[31]．

fluoxetineを40 mg経口投与した場合，Tmaxは6～8時間，Cmaxは15～55 ng/mLと報告されており，吸収に対する食事の影響は少ないと考えられている[30]．

fluoxetine，norfluoxetineの半減期は，単回投与の場合にそれぞれ1～3日，4～6日と比較的長い．継続投与の場合でともに4～6日と比較的長い．このため，fluoxetine中断後も数週間は体内に薬物が残存し，他の薬物との相互作用に注意が必要である[32]．

fluoxetineの主要な代謝酵素はCYP2C9であり，その他にCYP3 A3，CYP3 A4も関与しているとされている[33]（図❶-④）．

これまでの報告によると，高齢者においては若年者と比較した場合にfluoxetineの薬物動態に有意な変化はみられないようである[34]．また肝硬変患者において，fluoxetineの半減期が2～3日から平均7.3日に延長したという報告があり[21]，腎機能障害者ではfluoxetine 20 mgを2カ

月間投与してもfluoxetine，norfluoxetineの血中濃度は健常者と比較しても有意な差はなかったとされている[35]．

おわりに

SSRIの薬物動態と代謝についてフルボキサミン，パロキセチンを中心に概説した．わが国では，フルボキサミンが1999年に導入されて以来，従来の三環系抗うつ薬と比較して副作用が少なく，治療効果も同等であるなどの理由から，現在ではSSRIがうつ病治療の第一選択薬として使用されている．しかしその使用法については，臨床症状や副作用の出現などを評価することで用量の調整や他剤への変更などが判断されており，TDMなどの客観的な指標により体内薬物動態などを考慮して薬剤選択をおこなうなどの有用性についてはまだ認められていない．このような情報の蓄積や追証が今後の個別化薬物医療の実現にとって重要だと思われ，臨床に携わる者としては少なくとも体内での薬物動態を十分に理解し，SSRIの利点をより引き出せるようにしておくことが必要である．

（須貝拓朗/澤村一司/染矢俊幸）

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A Candidate Pathway Strategy for Integration of Pharmacogenomic Components of Variability in Antipsychotic Treatment Outcomes: A Focus on Aripiprazole

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Abstract: Aripiprazole is the first atypical antipsychotic introduced to medical practice with partial dopamine-serotonin agonist properties. Other new molecular entities such as bifeprunox, a partial agonist at the dopamine D2 and serotonin 5-HT_{1A} receptors, are currently being evaluated in early stage drug development as potential antipsychotic agents. As a partial agonist, whether aripiprazole displays an agonist effect or attenuates dopaminergic neurotransmission may depend on regional variations in endogenous dopamine tone. Hence, aripiprazole offers a therapeutic advantage to differentially modulate dopaminergic activity in brain regions in a graded fashion. This mechanism of action is intriguing when considered in the context of the dopamine hypothesis of schizophrenia whereby positive symptoms (e.g. hallucinations and delusions) are associated with increased mesolimbic dopaminergic activity while reduced activity in mesocortical dopaminergic pathways underlies negative symptoms (e.g. avolition and anhedonia) and cognitive deficits. Despite its therapeutic promise, antipsychotic response to aripiprazole is highly variable, and some patients do not respond at all to drug therapy. Treatment-emergent adverse events associated with aripiprazole include insomnia, anxiety, akathisia or worsening of psychosis in some patients. These observations suggest that the underlying mechanism of action of aripiprazole in psychotic disorders is more complex than what would be anticipated solely by simple partial agonist effects at the dopamine D2 receptor. For example, while aripiprazole attenuates dopaminergic hyperactivity it does not increase locomotor activity in reserpinized (hypodopaminergic) rats, which is not fully consistent with a partial agonist mode of action.

Aripiprazole can induce a diverse range of effects at dopamine D2 receptors (agonism, antagonism, partial agonism) depending on the cellular milieu defined by promiscuous interactions with a host of signaling partners and variability in local G protein complement and concentration. This diversity provides an opportunity to illustrate the importance of integrating data on genetic variation in pharmacokinetic pathways and molecular targets for antipsychotics including biogenic amine receptors and their downstream signaling partners. Theragnostics, a new subspecialty of molecular medicine formed by combination of therapeutics with diagnostics, offers the potential to synthesize different types of biomarkers (DNA and protein-based) in the context of antipsychotic treatment outcomes. Because the dopamine receptor genetic variation is extensively reviewed elsewhere, we discuss the pharmacogenomic significance of variability in genes encoding for the 5-HT_{1A} (*HTR1A*) and 5-HT_{2A} (*HTR2A*) receptors and CYP2D6- and CYP3A4-mediated aripiprazole metabolism. As the field moves toward predictive genetic testing for newer antipsychotics, we emphasize the need for collaboration among pharmacogeneticists, bioethicists and specialists in science and technology studies.

Key Words: Aripiprazole, OPC-14597, pharmacogenomics, atypical antipsychotics, genetic biomarkers, personalized therapeutics, CYP2D6, CYP3A4, HTR1A, HTR2A, bioethics.

1. INTRODUCTION

The discovery of chlorpromazine in 1952 led to development of typical antipsychotics with full antagonistic properties at the dopamine D2 receptor for the treatment of schizophrenia and other psychotic disorders. Over the past two decades, serotonin/dopamine antagonists such as clozapine signaled the development of a second wave of "atypical" antipsychotic compounds that displayed enhanced drug safety profiles, most notably through reduction of risk for extrapyramidal symptoms (EPS), as well as improvements in negative symptoms and cognitive deficits of schizophrenia [Marder *et al.* 2002].

Aripiprazole is the latest atypical antipsychotic introduced to medical practice [Davies *et al.* 2004]. In contrast to

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previous atypical antipsychotics that act as full antagonists at the serotonin and the dopamine receptors, aripiprazole displays partial agonist actions on the dopamine D2, D3 and the serotonin (5-hydroxytryptamine, 5-HT) 5-HT_{1A} receptors and antagonist effects on the 5-HT_{2A} receptor [Aihara *et al.* 2004; Shapiro *et al.* 2003; Jordan *et al.* 2002; Lawler *et al.* 1999]. The renewed optimism for the treatment of schizophrenia, in large part driven by the availability of atypical antipsychotics, has been hampered by the emergence of a new class of side effects typified by excessive weight gain and disturbances in lipid and glucose homeostasis [Nasrallah and Newcomer, 2004]. In addition, similar to conventional antipsychotics, 20% to 30% of patients treated with atypical antipsychotics fail to respond while other patients may be noncompliant to therapy due to weight gain or concerns for drug safety. To this end, it is noteworthy that recent systematic reviews of clinical trials have further reframed the current thinking on aripiprazole and the broader discussions on the effectiveness and safety of atypical antipsychotics [Stip, 2002]. For example, Leucht *et al.* [2003] conducted a meta-analysis of randomized controlled trials where atypical antipsychotics were compared with low-potency (equivalent or less potent than chlorpromazine) typical antipsychotics. They found that mean doses of chlorpromazine at less than 600 mg/day or its equivalent had no higher risk of EPS than new generation drugs [Leucht *et al.* 2003]. An earlier meta-regression analysis by Geddes *et al.* [2000] of more than 12,000 patients drawn from 52 randomized trials comparing atypical (amisulpride, clozapine, olanzapine, quetiapine, risperidone, and sertindole) and typical antipsychotics (e.g. haloperidol or chlorpromazine) suggested that the risk-benefit ratio of typical antipsychotics may approach that observed with newer generation antipsychotics when the former are used at an optimal dose or concentration. Meta-analyses may not, however, able to identify drug effects in 'niche' populations or qualitative measures of therapeutic outcomes expressed by the patients [Kapur and Remington, 2000; Kerwin, 2001]. Nonetheless, these data collectively point toward the importance of developing biomarkers, or predictive tests that can better delineate the patient subpopulations wherein aripiprazole and the new generation atypical antipsychotics may display improved therapeutic efficacy and further differentiation from older typical antipsychotics.

It is notable that numerous lead compounds are presently being evaluated in clinical trials as atypical antipsychotic candidates for therapeutic use in schizophrenia, bipolar disorder or other psychotic disorders [Grady *et al.* 2003]. For example, bifeprunox (DU-127090) is another partial agonist at dopamine D2 (K_i = 3.2 nM) and 5-HT_{1A} (K_i = 10.0 nM) receptors but appears to be devoid of activity at the 5-HT_{2A} receptor [Lieberman, 2004]. In this regard, the End-of-Phase 2A (EOP2A) meetings between the regulatory agencies and the pharmaceutical industry are becoming an essential step before critical [go/no-go] decisions are made to proceed with costly confirmatory large-scale phase 3 trials [Ozdemir *et al.* 2005]. Hence, focused phase 1 and phase 2A trials in patients identified with biomarkers that predict a higher likelihood of therapeutic response can markedly facilitate the EOP2A reviews by rational selection (or attrition) of new antipsychotic candidates and drug development timelines [Ozdemir and Lerer, 2005].

Pharmacogenomics is the study of the role of genetics on inter-individual and between population variability in drug effects, using a broad survey of the human genome [Kalow, 2002; Evans and McLeod, 2003; Malhotra, 2003]. According to the definitions provided by the US National Institutes of Health expert working group, a biological marker (biomarker) is a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacological responses to a therapeutic intervention [Biomarkers Definitions Working Group, 2001]. Customization of antipsychotic drug therapy by pharmacogenomic biomarkers is an area of growing interest in clinical psychiatry [Collier, 2003; Lahdelma and Koskimies, 2004; Malhotra, 2004]. Initial investigations in the field of psychiatric pharmacogenomics dealt with cross sectional patient samples based on retrospective study designs and focused on candidate genes concerned primarily with drug metabolism and pharmacokinetic elements. These studies provided an important baseline assessment for the clinical promise of pharmacogenomic research that would lead toward personalized prescribing [Kalow, 1962; Daly, 2004]. Increasingly, genetic variability in a broader array of molecular drug targets (pharmacodynamics) and their relevance for psychotropic drug efficacy and safety are being studied [Masellis *et al.* 1995; Nebert, 2000; Lerer, 2002; Lerer and Macciardi, 2002; Pickar, 2003; Reidenberg, 2003]. Yet despite numerous reports in the literature concerning pharmacogenomic associations with antipsychotic drug response phenotypes, there remains a lamentable gap in pharmacogenomic research at the point of patient care to translate these findings into genetic tests and therapeutic policy or treatment guidelines [Nebert *et al.* 2003; Albers and Ozdemir, 2004]. Moreover, strategies for optimal study design (and the attendant barriers) on how best to integrate pharmacogenomic information on pharmacokinetic and pharmacodynamic variability in the field of psychiatric pharmacogenomics are in need of further evaluation.

Pharmacogenomic investigations of antipsychotic treatment outcomes have focused largely on the prototype atypical antipsychotic clozapine. There is a paucity of clinical pharmacogenomic data with other atypical antipsychotics [de Leon *et al.* 2005]. It is not yet clear whether the genetic biomarker findings that have emerged from studies with clozapine are drug specific or are applicable to other newer antipsychotic agents. The reader is referred to existing comprehensive reviews on pharmacogenomics of clozapine and other serotonin-dopamine antagonist antipsychotics [Correll and Malhotra, 2004; Malhotra *et al.* 2004; Ozaki, 2004; Scharfetter, 2004]. In the present overview, we discuss instead the pharmacological mechanism of action of aripiprazole as an example of a new class of antipsychotic drug with functionally selective effects on dopamine D2 receptors and significant interactions with selected biogenic amine receptors [Shapiro *et al.* 2003]. By examining the case of aripiprazole and its proposed mode of action in psychotic disorders, we review the potential sources of genetic variation in primary pharmacodynamic and pharmacokinetic

candidate pathways that are likely to play a role in therapeutic response to aripiprazole.

2. GENETIC VARIATION IN DRUG TARGETS AND PHARMACOKINETIC PATHWAYS

2.1. Candidate Pathway Approach to Pharmacogenomic Study Design: A Balanced Compromise Between Statistical Power and Scope of Genetic Inquiry

Investigations into the genetic basis of individual variability in drug response started with the discipline of pharmacogenetics [Motulsky, 1957; Kalow, 1962; Kalow, 2002]. These early pharmacogenetic studies focused on candidate SNPs or a limited number of genes. More recent research, however, has clearly demonstrated that the hereditary components of drug effects are often polygenic [Evans and McLeod, 2003; Ozdemir *et al.* 2005]. With the impetus provided by the Human Genome Project (HGP) and the acceleration in the development of high throughput genomic technologies, it became possible to begin exploring complex polygenic factors involved in drug function, variability and disease etiology. An editorial in the September 1997 issue of Nature Biotechnology [Marshall, 1997] introduced, for the first time, the term pharmacogenomics into the research literature [see Hedgecoe, 2003; for a detailed account of the history of evolution of pharmacogenetics/ pharmacogenomics and related biotechnologies]. Although both pharmacogenetics and pharmacogenomics share essentially the same goal of identifying the genetic basis of variability in drug effects, pharmacogenomics takes a broader scope of inquiry, usually on a genome-wide scale. Over the past several years, a number of researchers from the fields of biological psychiatry, human genetics, pharmacology, and bioinformatics have played important roles in the development of the discipline of pharmacogenomics and its applications to clinical medicine. As research on the genetic basis of individual differences in response to atypical antipsychotics and other psychotropic drugs continues to evolve, a number of issues pertinent for the optimal design of study protocols (e.g. the use of haplotypes, genomic controls or strategies for unequivocal description of pharmacological phenotypes) have been described and discussed in detail [Devlin and Roeder, 1999; Bacanu *et al.* 2000; Nebert *et al.* 2003]. Notably, the interpretation of genetic studies of many common complex diseases have been streamlined in 1990s by specific criteria outlined to prevent false positive claims and standardized reporting of linkage results [Lander and Kruglyak, 1995]. Hence, there are lessons that may be drawn from previous experiences dealing with genetics of human diseases [Jorde, 2000]. We herein focus our discussion on how best to harness the promise of pharmacogenomics in therapeutic decisions relating to atypical antipsychotic medications through the integration of molecular genetic data from pharmacokinetic and pharmacodynamic candidate genes.

A typical characteristic of pharmacogenomic studies is the increase in the scope of queried genetic loci. Despite the initial well-deserved enthusiasm for pharmacogenomics in clinical psychiatry, the increased ability of the researchers to characterize multiple genes brings with it a statistical conundrum. In order to allow statistical correction for multiple comparisons in treatment outcomes among various genes or genetic loci, an adequate number of patients - on the order of several thousands - has to be recruited in clinical pharmacogenomic studies. As an alternative, hypothesis testing in small samples of patients, studies with candidate genes chosen by a careful consideration of the disease biology, pharmacokinetics or molecular drug targets have been advocated. On the other hand, candidate gene studies are open to criticism as they may neglect the important contributions of genes located upstream or down-stream the biological pathway where the primary candidate gene of interest is being investigated.

To address the concerns about the scope of molecular genetic analysis and the issue of sample sizes that can be realistically attained in clinical pharmacogenomic studies, a "candidate pathway" approach is being advocated [Fourie and Diasio, 2005]. In this approach, all or most genes positioned on a biological pathway are considered. For example, in the serotonin or dopamine system, it would be necessary to analyze genes encompassing neurotransmitter synthesizing enzymes, neurotransmitter receptors, transporters and the enzymes that contribute to degradation of the neurotransmitter molecules (see Fig. 1). Evans and McLeod [2003] have recently provided a theoretical illustration of the utility of evaluating genotypic data in tandem, from drug-metabolism and drug-receptor related pathways, yielding therapeutic indexes (efficacy:safety ratios) ranging from 13 to 0.125 (Fig. 2). Note, for example, that the same drug concentration (e.g. AUC = 200) may lead to markedly different percentage of patients responding to therapy depending on the molecular genetic variation in the target receptor pathway (*middle panel* in Fig. 2). Conversely, for each genetic subtype of a receptor, different drug concentrations result in varying degrees of therapeutic response and toxicity, illustrating the importance of controlling for genetic or environmental sources of variability in drug metabolism, pharmacokinetics and molecular drug targets in pharmacogenetic association studies.

Using the candidate pathway approach, it should therefore be emphasized that there is much theoretical basis for a joint investigation of genetic variability in pharmacokinetic and/or serotonin-dopamine neurotransmitter pathways that may underlie response to aripiprazole. For example, genetic differences in aripiprazole metabolism mediated by CYP2D6 as well as the primary neurotransmitter receptor targets for aripiprazole (e.g. 5-HT_{1A}, 5-HT_{2A}, and dopamine D2 receptors) can now be investigated in concert with pharmacogenomic studies, as outlined in the subsequent sections.

The search for genetic biomarkers of response to aripiprazole may also carry the risk for excessive compartmentalization of various other biomarkers that may otherwise provide complementary information. As with the need to bridge genetic biomarker data from multiple candidate pathways noted above, it will be necessary to integrate biomarkers of response to atypical antipsychotics along the biological cascade from genes to their expressed products including the encoded proteins. Because the only barrier between the patient and antipsychotic safety or efficacy may rely on the accuracy of a pharmacogenomic test, clinicians need to know both the genetic variants in

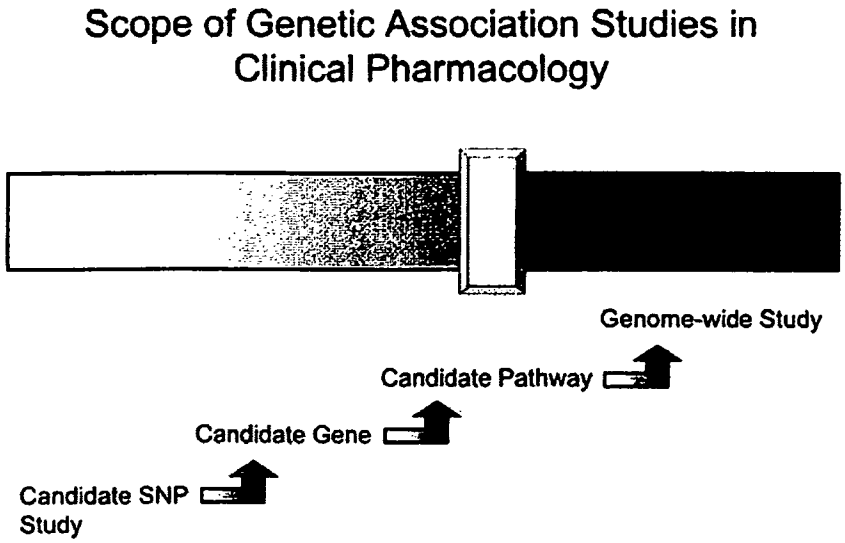

Fig. (1). The scope of molecular genetic analyses in clinical pharmacogenomic association studies ranging from candidate SNP (feasible in limited samples of study subjects) to genome wide investigations (typically in very large samples in the order of hundreds to several thousand patients). A realistic scope of genetic inquiry, in the form of candidate pathway approach, is depicted by the vertical column on this spectrum.

patients' DNA as well as the corresponding protein function. This is essential because (1) proteins are responsible for the eventual functional or clinical significance of genes and, (2) there may be marked differences or fluctuations in protein function (than what is predicted solely by gene structure) due to environmental factors or endogenous physiological rhythms that may influence posttranscriptional/ posttranslational modifications of gene products and proteins. Further, most drug effects are elicited within a matter of minutes, hours or days which may demand a more precise prediction of the present or acute state of the pathophysiological pathway whose function is inferred through a genetic test. Hence, an accurate prediction of antipsychotic treatment outcomes may require a two-step complementary strategy involving both genetic and proteomic tests for the same gene and its protein product, respectively. To this end, there is reason for guarded optimism that theragnostics, a new subspecialty of molecular medicine formed by combination of therapeutics with diagnostics, may allow the synthesis of different types of biomarker data (DNA and protein-based) in the context of antipsychotic therapeutics [Funkhouser, 2002].

3. MOLECULAR TARGETS FOR ARIPIPRAZOLE: MODE OF ACTION IN PSYCHOSIS

3.1. A Move Towards Partial Dopamine Agonists for Treatment of Schizophrenia

The dopamine hypothesis of schizophrenia is predicated on the idea that the positive symptoms of psychosis (e.g. delusions and hallucinations) are in part attributable to an *elevated* dopaminergic activity in the mesolimbic pathway, while *reduced* activity in the mesocortical dopaminergic pathway projecting to the frontal cortex is responsible for the negative symptoms (e.g. avolition and anhedonia) and neurocognitive deficits [Carlsson *et al.* 2004; Lieberman, 2004]. Hence, drugs that can differentially modulate dopaminergic activity in these brain regions would be ideal for alleviating both positive and negative symptoms of schizophrenia.

Strategies in antipsychotic drug development have recently witnessed a shift in emphasis from dopamine-serotonin antagonists, a prime focus of the pharmaceutical industry in 1990s, to dopamine partial agonists with the introduction of aripiprazole in November 2002 by the US Food and Drug Administration [Abilify®, 2002; Carlsson *et al.* 2004]. Because partial agonists by definition have lower intrinsic activity than the endogenous ligands (e.g. dopamine), aripiprazole attenuates dopaminergic neurotransmission in the presence of increased dopaminergic tone while acting as an agonist in synapses with reduced dopaminergic function [Stahl, 2001; Tamminga, 2002]. Moreover, partial agonists may prevent complete blockade of neurotransmission in brain regions with normal dopaminergic activity, thereby reducing the risk for extrapyramidal side effects. Atypical antipsychotics with partial agonist properties at dopamine receptors therefore offer the possibility of being able to modify or 'stabilize' dopaminergic neurotransmission in a graded and nuanced fashion depending on the existing dopaminergic tone in each brain region. By contrast, typical antipsychotics that act as full antagonists at dopamine D2 receptors lead to less desirable "on" or "off" regulation of synaptic function in all brain regions that project or receive dopaminergic innervation (see also Section 3.3 on alternative explanations on the mode of action of aripiprazole, and the "Functional Selectivity

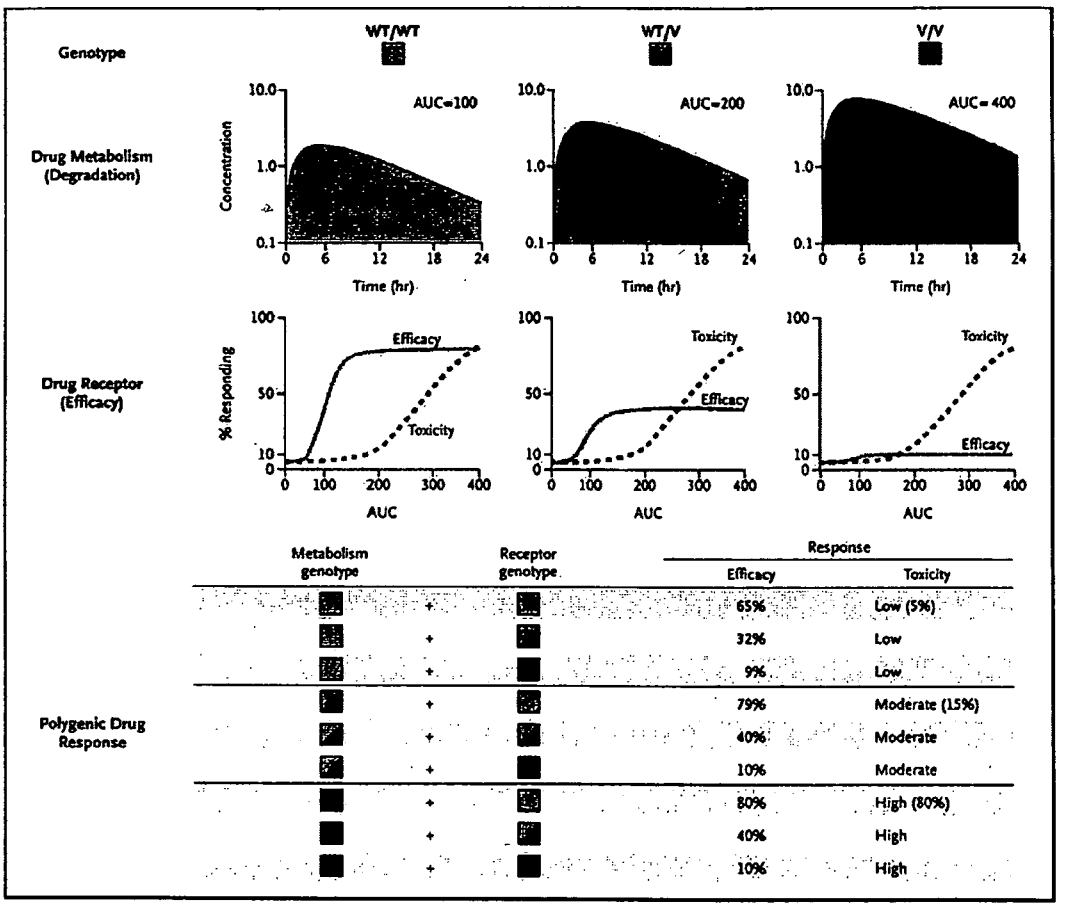

Fig. (2). A conceptual framework for genetic variability in drug metabolism and drug targets, and their integrated influence on response to pharmacotherapy. Two genetic polymorphisms, one in a drug metabolizing enzyme (*top panel*) and the second in a drug receptor (*middle panel*), depict differences in drug clearance (or the area under the plasma concentration–time curve [AUC]) and receptor sensitivity in patients who are homozygous for the wild-type allele (WT/WT), are heterozygous for one wild-type and one variant (V) allele (WT/V), or have two variant alleles (V/V) for the two polymorphisms. The *bottom panel* displays the nine potential combinations of drug-metabolism and drug-receptor genotypes and the corresponding drug-response phenotypes calculated from data at the top. "reprinted with permission from Evans & McLeod, 2003".

Hypothesis" proposed by Lawler *et al.* 1999 and Shapiro *et al.* 2003).

3.2. Aripiprazole Chemistry and Structure-Activity Relationship

Antagonism of postsynaptic dopamine D2 receptors appears to be essential not only for antipsychotic efficacy against positive symptoms of schizophrenia but also contributes to debilitating neurological side effects such as EPS [Lieberman, 2004]. OPC-4392, the predecessor of aripiprazole (OPC-14597), was initially synthesized to modulate dopaminergic neurotransmission indirectly by way of an alternate mechanism through the stimulation of presynaptic dopamine D2 autoreceptors [Yasuda *et al.* 1988]. This therapeutic strategy was based on the idea that dopamine autoreceptors serve as part of an inhibitory feedback mechanism regulating dopamine synthesis and release from the presynaptic nerve terminals. The relatively weak effects of OPC-4392 on the postsynaptic dopamine receptors led to interest in the synthesis and development of compounds such as aripiprazole that have dual actions on both the pre- and postsynaptic dopamine receptors [Kikuchi *et al.* 1995]. As a quinolinone derivative, aripiprazole differs from its structurally related predecessor OPC-4392 by two chloro substituents at positions 2 and 3 of the phenyl-

piperazinyl moiety. The halogen replacement of the phenylpiperazinyl ring is thought to increase the potency of antagonist effects on the postsynaptic dopamine receptors [Kikuchi *et al.* 1995; Oshiro *et al.* 1998; Ozdemir *et al.* 2002]. The affinities of aripiprazole toward the [^{3}H]spiperone-labeled D2 receptors in the rat frontal cortex, limbic forebrain and striatum are about 7- to 20-fold higher than OPC-4392 [Kikuchi *et al.* 1995]. Notably, aripiprazole acts as an antagonist at the postsynaptic D2 receptors at doses that produce agonist effects at the presynaptic dopaminergic nerve terminals [Kikuchi *et al.* 1995; Oshiro *et al.* 1998]. In contrast, the ED_{50} values for the biological effects of OPC-4392 as a presynaptic dopamine autoreceptor agonist and postsynaptic dopamine receptor antagonist differ by two orders of magnitude, thereby constraining the possibility of a simultaneous dual pharmacological action on both dopamine autoreceptors and those located on the postsynaptic membrane [Oshiro *et al.* 1998].

3.3. Aripiprazole Mode of Therapeutic Action in Psychosis

Aripiprazole displays partial agonist activity on the dopamine D2, D3 and the serotonin 5-HT_{1A} receptors and antagonist effects on the 5-HT_{2A} receptor with K_i values of 3.3, 1.0, 5.6 and 8.7 nM, respectively [Shapiro *et al.* 2003]. *In vitro* receptor binding studies suggest that aripiprazole has high affinity for several other neurotransmitter receptors such as 5-HT_{2B} (K_i = 0.4 nM) and 5-HT_7 (K_i = 10.3 nM) [Shapiro *et al.* 2003].

Aripiprazole dose-dependently inhibits apomorphine-induced stereotypy (an *in vivo* model of dopaminergic hyperactivity) in animals [Kikuchi *et al.* 1995; Semba *et al.* 1995]. In contrast to typical antipsychotics, the latter effect of aripiprazole is observed at doses (ED_{50} = 12 μmol/kg, po) about one order of magnitude lower than that which produces catalepsy (ED_{50} = 150 μmol/kg, po) [Oshiro *et al.* 1998]. Catalepsy has been used as a valid preclinical model for detecting the EPS liability of compounds in humans. For aripiprazole, its weak cataleptogenic effect in animal models appears to correlate well with the lower incidence of EPS in patients treated with aripiprazole [Marder *et al.* 2003].

By virtue of partial dopamine agonist properties, aripiprazole has lesser agonist effects than the endogenous naturally occurring ligand dopamine. It has been suggested that aripiprazole acts as an agonist, or a *functional* antagonist attenuating dopaminergic neurotransmission depending on the endogenous neurotransmitter concentration at the receptor-ligand biophase as well as the receptor reserve on the neuronal membrane [Lieberman, 2004; Tadori *et al.* 2005]. The dopamine autoreceptors are strategically positioned at both the presynaptic nerve terminus and the neuronal soma occurring as somatodendritic receptors. The *agonist* effects of aripiprazole on these dopamine autoreceptors are attributed in part to the high receptor reserve in the presynaptic nerve terminus and the lower (than the synaptic cleft) dopamine concentration in the vicinity of the somatodendritic autoreceptors [Lieberman, 2004]. Consistent with these theoretical considerations, aripiprazole exerts agonistic effects on the inhibitory dopamine autoreceptors as reflected by the blockade of compensatory increase in dopamine synthesis in reserpine treated rats [Kikuchi *et al.* 1995]. Excitability of dopaminergic neurons in the ventral tegmental area as measured by the spontaneous firing of type 1 neurons is inhibited by aripiprazole treatment in rats [Momiyama *et al.* 1996]. Further evidence of this activity is reflected by its reversal of reserpine- and gamma-butyrolactone-induced increase in tyrosine hydroxylase activity in the mouse and rat brain [Kikuchi *et al.* 1995].

There are a number of observations, however, that are at variance with the proposed partial agonist effects of aripiprazole at dopamine D2 receptors. An *in vivo* micro-dialysis study in rats showed a decrease in extracellular dopamine concentration following aripiprazole treatment, but only at doses (10 and 40 mg/kg) markedly higher than those that produce behavioral effects in the animal models described above [Semba *et al.* 1995]. Moreover, aripiprazole did not influence behavioral measures indicative of postsynaptic dopamine receptor stimulation such as hyper-locomotion in mice treated with reserpine, or contralateral rotation in rats with unilateral striatal 6-hydroxydopamine lesions [Kikuchi *et al.* 1995]. Aripiprazole can induce a diverse range of effects at dopamine D2 receptors (agonism, antagonism, partial agonism) in different cell lines, or in the postsynaptic membrane and dopamine autoreceptors, depending on the cellular milieu defined by promiscuous interactions with a host of signaling partners and variability in local G protein complement and concentration [Lawler *et al.* 1999; Shapiro *et al.* 2003]. This ability of aripiprazole to elicit different functional effects at the same molecular isoform of the dopamine receptor expressed in different neuroanatomical or cellular locations has been referred to as the "Functional Selectivity Hypothesis" [Lawler *et al.* 1999; Shapiro *et al.* 2003], as an alternative to explanations based on a dopamine receptor partial agonist mechanism of action [Carlsson *et al.* 2004; Lieberman, 2004; Tamminga, 2002; Stahl, 2001]. To this end, it should be noted that the "Functional Selectivity Hypothesis" raises additional possibilities for future pharmacogenomic research: genetic variations in signaling partners for dopamine receptors may also contribute to individual differences in antipsychotic response to aripiprazole [Roth, 2000].

Aripiprazole and other atypical antipsychotics uniformly display a high affinity for the 5-HT_{2A} receptor, a property that may contribute to their reduced liability for EPS and tardive dyskinesia. For example, serotonergic neurons projecting from the dorsal raphe nuclei exert a tonic inhibitory control on the nigrostriatal pathway through 5-HT_{2A} receptors located on the dopaminergic neuronal soma in the substantia nigra and the nerve termini in the striatum. In effect, stimulation of the 5-HT_{2A} receptors on the nigrostriatal pathway results in a decrease in dopamine release in the striatum [Lieberman *et al.* 1998]. The blockade of 5-HT_{2A} receptors by antagonists such as aripiprazole counteracts the serotonergic inhibition of dopamine release. Hence, 5-HT_{2A} receptor antagonism can help offset the antipsychotic-induced reduction in dopaminergic function in the striatum and the basal ganglia where excessive blockade of dopamine function can lead to EPS.

Aripiprazole displays antipsychotic efficacy both for positive and negative symptoms of schizophrenia [Marder *et al.* 2003; DeLeon *et al.* 2004]. Despite these advantages, the extent and the time course of antipsychotic response to aripiprazole may vary considerably among patients. For example, in a 52-week trial assessing long-term efficacy, as defined by a 30% or more reduction in PANSS scores, about half of the patients could be classified as nonresponders [Kasper *et al.* 2003; DeLeon *et al.* 2004]. Advances in our understanding of pharmacogenomic factors that influence patient-to-patient variability in response to aripiprazole may thus contribute to rational prescription of partial dopamine receptor agonists in patients with schizophrenia. In addition, genetic biomarkers of anti-psychotic response may help to further differentiate aripiprazole from other atypical antipsychotics.

For antipsychotic safety related endpoints, the available clinical data thus far suggest that aripiprazole is not associated with a marked increase in prolactin levels and EPS associated with typical antipsychotics, nor does it appear to pose a significant risk for metabolic disturbances observed with other atypical antipsychotics [Swainston-Harrison and Perry, 2004]. We suggest, therefore, that the study of inter-individual variability in aripiprazole efficacy toward various clinical dimensions of schizophrenia may warrant priority over those phenotypes related to safety endpoints in future pharmacogenomic investigations.

Endophenotypes of psychotic disorders or intermediary biochemical and neuroimaging endpoints are receiving increasing attention in pharmacogenomics [Heinz *et al.* 2003; Noble, 2003; Reist *et al.* 2004]. For aripiprazole and partial receptor agonists, clinical interpretations of neuro-imaging findings may require additional considerations. For example, Yokoi *et al.* [2002] found that administration of aripiprazole in humans for 14 days led to a dose-dependent (0.5 to 30 mg/day) increase in dopamine D2 and D3 receptor occupancy of between 40% and 95% as measured by positron emission tomography (PET). In patients treated with typical antipsychotics, the risk of EPS increases at D2 receptor occupancies above 80% [Nyberg *et al.* 1998]. Interestingly, EPS was not observed with aripiprazole even at striatal D2 receptor occupancy values above 90%, likely attesting to its low intrinsic activity; further, this suggests that the endophenotypes dealing with *in vivo* receptor occupancy need to be complemented with other measures of treatment outcome in search for genetic biomarkers of aripiprazole response [Grunder *et al.* 2003].

Taken together, and from a clinical pharmacogenomic standpoint, individual variations in dopamine D2 or serotonin 5-HT_{1A} or 5-HT_{2A} receptor genes (*DRD2*, *HTR1A* and *HTR2A*, respectively) emerge as prime candidates for developing genetic biomarkers of therapeutic response (or failure) to aripiprazole treatment. It should be mentioned that other receptors such as 5-HT_{2B} and 5-HT_7 for which aripiprazole displays a high binding affinity may deserve additional attention as putative molecular targets. However, genetic variation in these receptors and their pathophysiological significance remain less well understood. Because genetic variability in dopamine D2 and D3 receptors has been reviewed in detail previously [Noble, 2003; Staddon *et al.* 2005], we focus our attention in this synopsis on recent advances in our understanding of genetic differences in *HTR2A* and *HTR1A* genes that are likely to impact the attendant receptor function and treatment response to aripiprazole. Pharmacogenomic variations in other elements of the serotonergic pathway are beyond the scope of the present review and can be found elsewhere [Veenstra-VanderWeele *et al.* 2000; Glatt *et al.* 2004].

3.4. Response to Aripiprazole and Genetic Variation in 5-HT_{2A} and 5-HT_{1A} Receptors

Aripiprazole is a high affinity (K_i = 8.7 nM) antagonist at the 5-HT_{2A}, a G protein-linked receptor that activates phosphoinositide hydrolysis [Shapiro *et al.* 2003]. Antagonism of the 5-HT_{2A} receptor is a shared pharmacological attribute of clozapine and other atypical antipsychotics [Meltzer *et al.* 2003]. Conversely, stimulation of the 5-HT_{2A} receptor by agonists such as lysergic acid diethylamide (LSD) can mimic psychosis, for example, by induction of hallucinations [Aghajanian and Marek, 1999]. The 5-HT_{2A} receptor gene, *HTR2A*, maps to chromosome 13q14.1-14.2. Pharmacogenomic studies of *HTR2A* have thus far concentrated on three single nucleotide polymorphisms (SNPs), one in the promoter (A-1438G) and two in the coding region (T102C, synonymous; His452Tyr, nonsynonymous) [Veenstra-VanderWeele *et al.* 2000]. Among these, the frequency of the commonly occurring 102C-allele of the T102C SNP in healthy controls was reportedly 58.3% in Caucasians of British origin and 45.9% in an Israeli sample [Spurlock *et al.* 1998; Segman *et al.* 2001]. Notably, T102C genetic variation in *HTR2A* was previously associated with antipsychotic response to clozapine, serotonin induced platelet aggregation, prolactin response to fenfluramine and for predisposition to tardive dyskinesia, a movement disorder associated primarily with typical antipsychotic drugs [Arranz *et al.* 1995; Segman *et al.* 2001; Reist *et al.* 2004; Ozdener *et al.* 2005]. In addition, some, but not all, genetic studies of schizophrenia suggest a possible association with *HTR2A* [Veenstra-VanderWeele *et al.* 2000]. Postmortem allele specific gene expression studies in the temporal cortex of normal individuals found a lower expression of the 102C-allele than the T102 variant in *HTR2A* [Polesskaya and Sokolov, 2002], although another postmortem study could not replicate this observation [Bray *et al.* 2004].

The T102C SNP is in complete linkage disequilibrium with the A-1438G SNP in the *HTR2A* promoter region [Spurlock *et al.* 1998; Segman *et al.* 2001]. A study of A-1438G and T102C polymorphisms found an association with 5-HT_{2A} receptor binding in postmortem brains [Turecki *et al.* 1999], but this finding could not be confirmed in another study [Kouzmenko *et al.* 1999]. The A-1438G polymorphism does not affect basal or protein kinase C-induced gene transcription in HeLa cells [Spurlock *et al.* 1998]. However, the A-1438G SNP is positioned upstream of two alternative promoters for the *HTR2A*. Using two reporter gene assays and cell lines that express endogenous 5-HT_{2A}, a recent study found that the promoter activity was higher in the presence of the A allele compared to the G allele [Parsons *et al.* 2004]. Due to the significance of the 5-HT_{2A} receptor in serotonergic neurotransmission and the high

frequency of the T102C and A-1438G SNPs in human populations, further studies are necessary to delineate the mechanisms by which these genetic polymorphisms may lead to differences in 5-HT_{2A} receptor function.

A less common His452Tyr SNP in the C-terminal region of the 5-HT_{2A} receptor (9% frequency for the 452Tyr-allele in Caucasians) was previously associated with 5-HT-induced intracellular calcium mobilization [Ozaki *et al.* 1997]. Thus, the His452Tyr genetic variation may also explain individual differences in pharmacological effects of aripiprazole on the 5-HT_{2A} receptor.

HTR1A is an intronless gene encoding the 5-HT_{1A}, a G protein-linked receptor expressed both on pre- and postsynaptic membranes, acting primarily by inhibition of adenylate cyclase activity. *HTR1A* maps to human chromosome 5q12.3. Interest in the 5-HT_{1A} receptor, and by extension in *HTR1A*, stems from its role in the pathophysiology of anxiety and affective disorders [Strobel *et al.* 2003; Lesch and Gutknecht, 2004]. For example, *HTR1A* knockout mice display increased anxiety [Parks *et al.* 1998]. *In vitro*, several clinically efficacious atypical antipsychotics (such as ziprasidone) have high affinity for the 5-HT_{1A} [Richelson and Souder, 2000], while clozapine displays partial agonist activity at this receptor [Newman-Tancredi *et al.* 1996; Richelson and Souder, 2000]. Moreover, the documented anxiolytic and antidepressant properties of the 5-HT_{1A} receptor agonists (e.g. buspirone) [Blier and Ward, 2003] suggest that *HTR1A* may serve as an ancillary molecular target for the development of antipsychotic drugs directed both at psychosis and mood disorders that can occasionally co-exist, for example, in schizoaffective disorder or psychotic depression.

Allelic variation in *HTR1A* coding sequence has been extensively studied in African-American and Caucasian populations [Glatt *et al.* 2004]. Although a number of rare or low frequency nonsynonymous SNPs were identified within the *HTR1A* coding region, their low abundance (<3% allele frequency) in these populations would require large patient samples to discern clinical significance for individualization of antipsychotic therapy with aripiprazole. In an earlier functional study of a low frequency Gly22Ser variant (0.2% in Caucasians), Rotondo *et al.* [1997] found that the rare 22Ser allele did not influence receptor binding profile, although this variant was insensitive to receptor down-regulation [Nakhai *et al.* 1995]. 5-HT_{1A} receptor concentration-response curves were not influenced by the Ile28Val SNP, another rare nonsynonymous variant (0.55% in Caucasians) [Bruss *et al.* 1995; Nakhai *et al.* 1995].

Recently, Lemonde *et al.* [2003] proposed a transcriptional model for a new functional C(-1019)G SNP, located in a 26-bp palindrome, that binds transcription factors such as NUDR (nuclear deformed epidermal autoregulatory factor (DEAF-1)) in the transcriptional control region of the *HTR1A*. Interestingly, the (-1019)G variant of this SNP abolished the repression of 5-HT_{1A} autoreceptor expression, thereby leading to reduction in serotonergic neurotransmission. The regulatory C(-1019)G SNP of the *HTR1A* occurs in high frequency in the population. In Ontario, Canada, for example, the (-1019)G allele frequency was 37.3% in healthy controls of predominantly Caucasian descent [Lemonde *et al.* 2003]. A spectrum of psychopathologies ranging from schizophrenia to substance abuse [Huang *et al.* 2004] as well as therapeutic response to tricyclic and selective serotonin reuptake inhibitor antidepressants [Lemonde *et al.* 2004; Serretti *et al.* 2004], appear to be associated with the *HTR1A* C(-1019)G allelic variation. We suggest, therefore, that *HTR1A* genetic variation deserves further study in future clinical pharmacogenomic studies, particularly in relation to the clinical effects of aripiprazole on affective dimensions of psychopathology co-morbid with schizophrenia.

4. PHARMACOKINETICS OF ARIPIPRAZOLE AND PHARMACOGENETIC VARIATION

There are limited published data on mechanisms of inter-individual variability in aripiprazole pharmacokinetics [Mallikaarjun *et al.* 2004; Raggi *et al.* 2004]. The absolute oral bioavailability of aripiprazole is reportedly 87% [Abilify®, 2002]. After a single oral dose of [^{14}C]-labeled aripiprazole, less than 1% of the dose is excreted as unchanged parent drug in the urine while about 18% is recovered unchanged in the feces. In healthy male volunteers, aripiprazole displays linear pharmacokinetics at doses ranging from 5 mg to 30 mg daily. In healthy volunteers, the coefficient of variation (CV) for area under the plasma concentration-time curve (AUC_{0-24}) and the elimination half-life ($t_{1/2}$) at a dose of 20 mg/day was 51% and 34%, respectively [Mallikaarjun *et al.* 2004]. It should be noted that the extent of variability in aripiprazole disposition in patients with schizophrenia or other populations under real life clinical settings deserves further investigations. *In vitro*, it appears that aripiprazole is not subject to metabolism by CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19 and CYP2E1 enzymes and does not undergo direct glucuronidation [Abilify®, 2002]. Conversely, the effects of aripiprazole (inhibition or induction) on drug metabolizing enzymes are not presently known.

The primary routes of aripiprazole metabolism are reportedly dehydrogenation, hydroxylation and N-dealkylation [Abilify®, 2002], but virtually no information is available in the public domain on the relative quantitative or clinical significance of these metabolic pathways. Both CYP2D6 and CYP3A4 enzymes appear to contribute to formation of the dehydrogenated metabolite which, according to the drug label by the manufacturer, exhibits activity at the dopamine D2 receptor similar to the parent compound [Abilify®, 2002]. The AUC for the active dehydrogenated metabolite is about 40% of that for aripiprazole. To this end, the pharmacological activity profile of the dehydrogenated aripiprazole metabolite toward other neurotransmitter receptors is unknown.

CYP2D6 is one of the most extensively studied genetically polymorphic drug metabolizing enzymes with, for example, 7% of Caucasians classified as poor metabolizers (PMs) while the rest are extensive metabolizers (EMs) [Aklillu *et al.* 2002; Bertilsson *et al.* 2002; Ingelman-Sundberg, 2005]. Moreover, there are marked inter-ethnic variations in CYP2D6 catalytic function. In Asian populations (Chinese,