Chapter 2
Receptor Binding Targets for Antipsychotic Efficacy

Maureen M. Grainger, Rebecca Ahlbrand, Paul S. Horn, and Neil M. Richtand

Abstract In order to identify the contribution of individual serotonin and dopamine receptor subtype binding targets to antipsychotic medication efficacy, we analyzed correlations between binding affinity to cloned dopamine and serotonin receptor subtypes and clinically effective drug dose for atypical antipsychotic medications. The strongest correlation was observed between binding affinity to the D_3 subtype dopamine receptor and clinically effective atypical antipsychotic medication drug dose ($r=0.77$, $p=0.005$). In contrast, binding affinity to the D_2 ($r=0.59$, $p=0.056$) and D_4 subtype dopamine receptors ($r=0.23$, $p=0.23$) exhibited lower correlations with atypical antipsychotic medication dosages. No direct correlations were identified between atypical antipsychotic medication dose and binding affinities to serotonin 5-HT_{1A}, 5-HT_{2A}, 5-HT_{2C}, or 5-HT_7 receptor subtypes. Highly significant correlations were also observed between atypical antipsychotic medication dose and the ratios of D_2/5-HT_{1A} ($r=0.69$, $p=0.019$); D_3/5-HT_{1A} ($r=0.69$, $p=0.02$); $D_3 \times$ 5-HT_{2A} ($r=0.71$, $p=0.014$); ($D_2 \times D_3$)/5-HT_{1A} ($r=0.81$, $p=0.002$); ($D_2 \times D_3 \times$ 5-HT_7)/5-HT_{1A} ($r=0.74$, $p=0.010$); ($D_2 \times D_3 \times$ 5-HT_{2A})/5-HT_{1A} ($r=0.76$, $p=0.007$); ($D_2 \times D_3 \times$ 5-HT_{2C})/5-HT_{1A} ($r=0.76$, $p=0.007$); and ($D_2 \times D_3 \times$ 5-$HT_{2A} \times$

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5-HT_{2C})/5-HT_{1A} ($r = 0.72$, $p = 0.013$) receptor binding affinities. These observations suggest opposing interactions among three distinct domains of receptor binding targets contribute to the antipsychotic effects of atypical antipsychotic medications: (1) D_3 and D_2 dopamine receptor binding affinity enhance atypical antipsychotic medication potency. (2) Binding affinity to serotonin 5-HT_{2A}, 5-HT_{2C}, and 5-HT_7 receptors also facilitates antipsychotic efficacy. (3) In contrast, enhanced binding affinity to serotonin 5-HT_{1A} receptor reduces antipsychotic medication potency.

Keywords Dopamine • Serotonin • Schizophrenia • Psychosis • Neuroleptic • Antipsychotic

Abbreviations

5-HT	Serotonin
FDA	Food and Drug Administration
NIMH	National Institute of Mental Health
PDSP	Psychoactive Drug Screening Program

2.1 Introduction

Thirty-five years after Seeman and Creese published their seminal observations on the relationship between D_2 dopamine receptor binding affinity and antipsychotic medication potency [1, 2], mechanism(s) of action underlying the efficacy of antipsychotic medications continues to be a topic of interest and controversy [3–5]. Since the original observations of Seeman and Creese, each of the receptor targets for antipsychotic medications have been cloned, and binding data for each antipsychotic medication to the cloned human receptor is available. Additionally, recommended therapeutic dosages of antipsychotic medications have decreased substantially since those initial observations. Based on those developments, we analyzed the relationship between antipsychotic drug dose and binding affinity to cloned human dopamine and serotonin receptors [6]. That analysis suggested therapeutic efficacy for typical antipsychotic medications derived largely from D_2 dopamine receptor binding, while D_3 dopamine receptor binding affinity was not directly correlated to clinically effective dose for typical antipsychotic medications. Additionally, serotonin 5-HT_{1A} receptor binding inhibited potency for typical antipsychotic medications. In contrast, therapeutic efficacy for atypical antipsychotic medications was most highly correlated with combined effects of binding at D2, 5-HT_{2A}, and 5-HT_{2C} receptors, while serotonin 5-HT_{1A} receptor binding also inhibited potency for atypical antipsychotic medications. At the time of that earlier evaluation, full data was available for only seven atypical antipsychotic medications.

Since that initial analysis, four additional atypical antipsychotic medications have received FDA approval for therapeutic efficacy targeting psychotic symptoms in schizophrenia. The increase in sample size achieved by the addition of data for these newer medications increases the statistical power to identify relationships between receptor binding affinity and clinical potency for atypical antipsychotic medications. Additionally, there has been recent interest in potential therapeutic effects of serotonin 5-HT_7 antagonists in schizophrenia [7] as a result of data from preclinical studies examining effects of selective serotonin 5-HT_7 antagonists in animal models of relevance to psychotic and cognitive symptoms of schizophrenia [8–11]. Based upon those developments, we analyzed correlations between dopamine and serotonin receptor binding affinities, and clinically effective drug dose for 11 atypical antipsychotic medications with approved indications for the treatment of psychotic symptoms of schizophrenia.

2.2 Methods

Drug affinity K_i values determined by the NIMH Psychoactive Drug Screening Program (PDSP) [12] were used for data analysis, in order to minimize the influence of assay condition variability on receptor K_i values [13]. K_i values chosen for analysis were those listed as NIMH Psychoactive Drug Screening Program assay certified data, determined from assays using the cloned human receptors with drug of interest as test ligand. For K_i values for which PDSP certified assay data were not listed, the average K_i value from assay data compiled on the PDSP web site [12] using the cloned human receptor with drug of interest as the test ligand was utilized. K_i values from cloned human receptor for drug/receptor combinations not listed in the PDSP database were identified from published literature [14–16]. Tables 2.1 and 2.2 list K_i values used in our analysis along with data source. All binding data analyzed in our study has been previously reported, as described in Tables 2.1 and 2.2.

Average daily antipsychotic drug dose was determined from data in randomized, controlled clinical trials where possible [17], supplemented by the recommended dosage ranges from the ePocrates Rx drug reference guide (ePocrates, San Carlos, California). The midpoint of the dose range was utilized in subsequent calculations. Values for antipsychotic drug dose used in our analyses are included in Tables 2.1 and 2.2.

2.2.1 Data Analysis

Antipsychotic medication doses and binding affinities were log-transformed prior to analysis. Data were analyzed by Pearson correlation using GraphPad Prism software (GraphPad Software, Inc., La Jolla, CA) to test for correlations between antipsychotic doses and binding affinities for individual receptor subtypes and interactions between receptor subtypes. The linear correlation coefficient (r) is reported as a standardized measure of strength of association for each regression.

Table 2.1 Antipsychotic medication dopamine receptor K_i values

Drug	Clinically effective dose (mg)	K_i Values (nM)								
		D_1	D_2	D_2 short	D_2 long	D_3	D_4	$D_{4.2}$	$D_{4.4}$	D_5
Aripiprazole	10–15	387	0.95		*0.74*	4.5	*>1,000*			1,676
Asenapine	10–20	*8.85*	*8.9*	*8.84*	*8.9*	*9.38*	*8.95*			
Clozapine	300–600	189	431	*143.3*	*196*	646	*22.5*	*45.2*	*30*	235
Iloperidone	12–24	*216*	*3.5*	*13.3*	*6.3*	*10.55*	*13.75*		*21.37*	*319*
Lurasidone	40–80	***262***	***1.68***		***0.329;0.994***	***15.7***	***29.7***		***29.7***	
Olanzapine	10–15	58	72	*34.6*	*33.2*	63	*17.1*	*44.2*	*40.5*	90
Paliperidone	6	41.0	9.4			*2.6*	54.3			29
Quetiapine	150–750	712	567	*555*	*702*	483	*2,276*	*1,233*		1,738
Risperidone	1–4 mg	60.6	4.9	*4.73*	*6.0*	12.2	*7.12*	*16.7*	*26.3*	16
Sertindole	12–24		*4.14*	*5.8*	*4.87*	*5.76*	*9.29*	*17.67*		
Ziprasidone	140–160	30	4.0	*4.2*	*4.6*	17	*500.8*	*35.3*		152

Normal font PDSP certified data, *italic font* PDSP Ki database mean, *italic underlined* [16], *italic bold* [15], *italic bold underlined* [14]

Table 2.2 Antipsychotic medication serotonin receptor K_i values

Drug	Clinically effective dose (mg)	K_i Values (nM)											
		5-HT_{1A}	5-HT_{1B}	5-HT_{1D}	5-HT_{1E}	5-HT_{1F}	5-HT_{2A}	5-HT_{2B}	5-HT_{2C}	5-HT_{3}	5-$HT5_{A}$	5-HT_{6}	5-HT_{7}
Aripiprazole	10–15	5.6	833	63	8,000		*17.5*	*0.36*	*22.4*	628	1,241	574	10
Asenapine	10–20	*8.6*	*8.4*				*10.15*	*9.75*	*10.46*		*8.84*	*9.6*	*9.94*
Clozapine	300–600	105	398	2,132	966	*130*	*9.15*	*7.38*	*14.9*	241	3,857	17	18
Iloperidone	12–24	*93.21*	*89.12*	*15*			*1.94*		*146.99*	*10,000*		*63.09*	*112*
Lurasidone	40–80	***6.75***					***2.03***		***415***				***0.495***
Olanzapine	10–15	2,063	509	1,582	2,408	*310*	*4.90*	*11.8*	*14.2*	202	1,212	6.0	105
Paliperidone	6 mg	637.8	108.7	15.01	>10,000		1.9	61.86	*48*	>10,000	277.9	2,414	2.7
Quetiapine	150–750 mg	431	1,109	>10,000	2,402	*2,240*	*526*		*1,843*	>10,000	3,120	1,864	308
Risperidone	1–4 mg	427	53.6	29.2	>10,000	*1,240*	*0.481*	41.6	*33.4*	>10,000	205.8	2,241	6.6
Sertindole	12–24 mg	*280*	*60*	*96*	*430*	*360*	*0.387*		*0.9*			*5.4*	*28.*
Ziprasidone	140–160 mg	76	4	9	1,279		*0.73*		*13*	>10,000	291	61	6

Normal font PDSP certified data, *italic font* PDSP Ki database mean, *italic underlined* [16], *italic bold* [15]

2.3 Results

The correlation between average clinically effective antipsychotic dose and binding affinity to the cloned human D_2 receptor is illustrated in Table 2.3 and Fig. 2.1. Clinically effective dose and binding affinity to D_2 dopamine receptor were modestly correlated for second-generation antipsychotic medications ($r=0.59$, $p=0.056$). In contrast, average clinically effective atypical antipsychotic medication dose and binding affinity to the cloned human D_3 receptor are highly correlated [($r=0.77$, $p=0.005$), Table 2.3 and Fig. 2.1]. Average clinically effective atypical antipsychotic medication dose and binding affinity to the cloned human D_4 receptor are not correlated [($r=0.23$, $p=0.23$), Table 2.3 and Fig. 2.2].

The relationship between average clinically effective antipsychotic dose and binding affinity to the cloned human 5-HT_{1A}, 5-HT_{2A}, 5-HT_{2C}, and 5-HT_7 receptors is shown in Table 2.3. No direct correlations were identified between atypical antipsychotic medication dose and binding affinities to these serotonin receptor subtypes.

In order to evaluate possible interactions between receptor subtypes playing a role in mechanism of antipsychotic efficacy, we analyzed correlations between log (average dose) and log (ratio of binding affinities) for combinations of individual receptor subtypes, as summarized in Tables 2.3, 2.4, 2.5 and 2.6. Significant correlations were identified between dose and D_2/5-HT_{1A} ($r=0.69$, $p=0.019$) and D_3/5-HT_{1A} binding affinity ratios ($r=0.69$, $p=0.020$) (Fig. 2.3). In contrast, there was not a significant correlation between clinically effective antipsychotic dose and D_4/5-HT_{1A} binding affinity ratio ($r=0.41$, $p=0.21$) (Table 2.3).

The relationship between receptor subtype binding and clinical efficacy was further evaluated for atypical antipsychotic medications using a more comprehensive set of binding affinity ratios. While there is not a universal consensus on this issue, it has previously been suggested that the antipsychotic effect of atypical antipsychotic medications results from a balance of inhibition at serotonin 5-HT_{2A}, 5-HT_{2C}, and dopamine D_2 receptors [18–21], coupled with simultaneous agonist effects at serotonin 5-HT_{1A} receptors [22–24]. In order to identify therapeutic benefits resulting from the interaction between simultaneous effects at these receptor subtypes, we

Table 2.3 Correlation between clinically effective antipsychotic dose and receptor binding affinity

D_2			D_3			D_4			5-HT_{1A}			5-HT_{2A}		
n	*r*	p value	n	*r*	p value	n	*r*	p value	n	*r*	p value	n	*r*	p value
11	.59	.056	**11**	**.77**	**.005**	11	.23	.23	11	.11	.76	11	.52	.10
5-HT_{2C}			5-HT_7			D_2/5-HT_{1A}			D_3/5-HT_{1A}			D_4/5-HT_{1A}		
n	*r*	p value	n	*r*	p value	n	*r*	p value	n	*r*	p value	n	*r*	p value
11	.33	.32	11	.23	.49	**11**	**.69**	**.019**	**11**	**.69**	**.020**	11	.41	.21

Bold font indicates p-value < 0.05

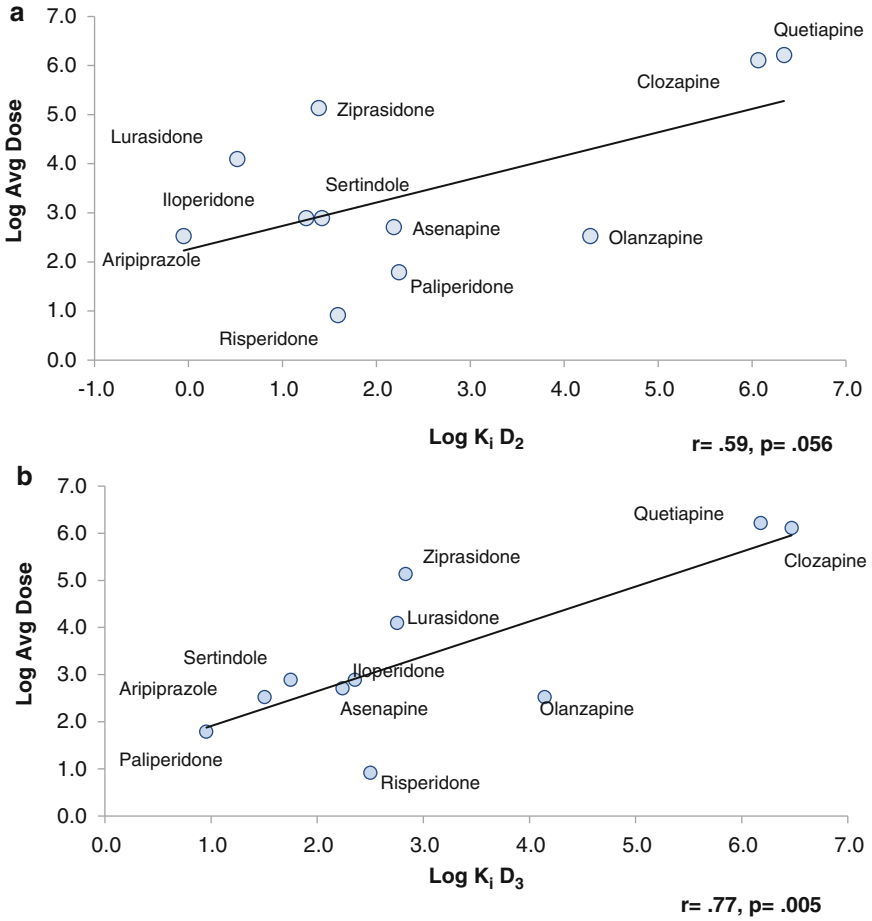

Fig. 2.1 Clinically effective atypical antipsychotic medication dose vs. binding affinity to cloned human dopamine D_2 (*upper panel*) and D_3 receptor (*lower panel*)

analyzed the relationship between clinically effective antipsychotic medication dose and ratios incorporating the binding affinities for each of these receptor systems. We also included serotonin 5-HT_7 receptor binding affinity in the data analysis. As shown in Table 2.4, atypical antipsychotic medication dose and binding affinity ratios to D_2 (5-HT_{2A}/5-HT_{1A}) ($r=0.66$, $p=0.027$) and D_3 (5-HT_{2A}/5-HT_{1A}) ($r=0.70$, $p=0.017$) are highly correlated. Similar correlations were observed between atypical antipsychotic medication dose and D_2 (5-HT_{2C}/5-HT_{1A}) ($r=0.65$, $p=0.030$) and D_3 (5-HT_{2C}/5-HT_{1A}) ($r=0.64$, $p=0.033$) binding affinity ratios (Fig. 2.4).

Combining binding affinity at D_2, D_3, and 5-HT_{2A} receptors identifies a significant correlation between these variables and clinically effective antipsychotic medication dose ($D_2 \times D_3 \times$ 5-HT_{2A}, $r=0.70$, $p=0.018$, Table 2.4). Modifying the relationship

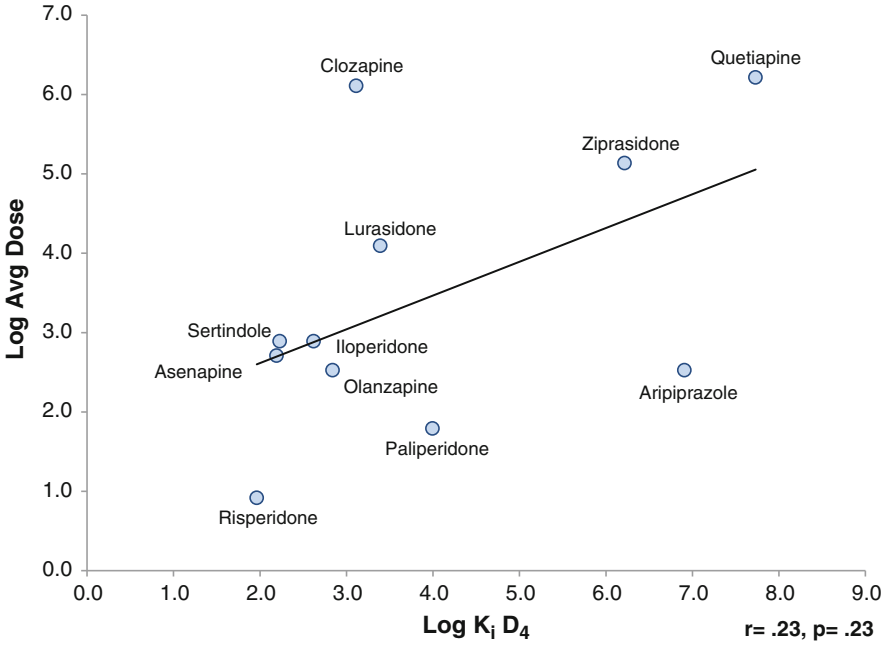

Fig. 2.2 Clinically effective atypical antipsychotic medication dose vs. binding affinity to cloned human dopamine D_4 receptor

via the inclusion of a functionally opposing role for serotonin 5-HT_{1A} receptor (i.e. $D_2 \times D_3 \times$ 5-HT_{2A}/5-HT_{1A}) strengthens the resulting degree of correlation (Table 2.5). Similar results were observed by including or omitting terms for serotonin 5-HT_{1A} receptor effects on the combined binding affinity at D_2, D_3, and 5-HT_{2C} receptors ($D_2 \times D_3 \times$ 5-HT_{2C}, r = 0.69, p = 0.020; $D_2 \times D_3 \times$ 5-HT_{2C}/5-HT_{1A}, r = 0.76, p = 0.007, Fig. 2.5).

The receptor binding relationships can also be modified so that dopamine D_2 or D_3 and serotonin 5-HT_{1A} receptor binding no longer have functionally opposite roles, and D_2 or D_3 binding no longer has a functionally similar action as 5-HT_{2A} and 5-HT_{2C} binding, by inverting the serotonin receptor affinity terms [i.e., D_2 (5-HT_{1A}/5-HT_{2A}); D_2 (5-HT_{1A}/5-HT_{2C}); D_3 (5-HT_{1A}/5-HT_{2A}); and D_3 (5-HT_{1A}/5-HT_{2C}), Table 2.6, right two columns]. This modification completely eliminates the correlation between binding affinity ratio and drug dosage for atypical antipsychotic medications.

2.4 Discussion

The data presented above extend our prior analysis of the relationships between receptor binding affinity to dopamine and serotonin receptor subtypes, and clinically effective antipsychotic medication drug dosage [6]. These examinations

Table 2.4 Correlation between clinically effective antipsychotic dose and receptor binding affinity ratios

D_2 (5-HT_{2A}/5-HT_{1A})			D_2 (5-HT_{2C}/5-HT_{1A})			D_3(5-HT_{2A}/5-HT_{1A})			D_3(5-HT_{2C}/5-HT_{1A})			$D_2 \times D_3$			$D_2 \times D_3 \times$ 5-HT_{2C}		
n	*r*	p value	n	*r*	p value	n	*r*	p value	n	*r*	p value	n	*r*	p value	n	*r*	p value
11	**.66**	**.027**	**11**	**.65**	**.030**	11	.70	.017	**11**	**.64**	**.033**	**11**	**.69**	**.018**	**11**	**.69**	**.020**
D_2(5-HT_{2A}/5-HT_7)			D_3(5-HT_{2A}/5-HT_7)			D_2(5-HT_7/5-HT_{1A})			D_3(5-HT_7/5-HT_{1A})			$D_2 \times D_3 \times$ 5-HT_7			$D_2 \times D_3 \times$ 5-HT_{2A}		
n	*r*	p value	n	*r*	p value	n	*r*	p value	n	*r*	p value	n	*r*	p value	n	*r*	p value
11	**.62**	**.042**	**11**	**.70**	**.016**	11	.66	.029	**11**	**.70**	**.016**	**11**	**.61**	**.048**	**11**	**.70**	**.018**

Bold font indicates p-value < 0.05

Table 2.5 Correlation between clinically effective antipsychotic dose and receptor binding affinity ratios

$(D_2 \times D_3)/5\text{-}HT_{1A}$			$(D_2 \times D_3)/5\text{-}HT_7$			$(D_2 \times D_3 \times 5\text{-}HT_{2A})/5\text{-}HT_{1A}$			$(D_2 \times D_3 \times 5\text{-}HT_{2C})/5\text{-}HT_{1A}$		
n	*r*	p value	n	*r*	p value	n	*r*	p value	n	*r*	p value
11	**.81**	**.002**	**11**	**.69**	**.018**	**11**	**.76**	**.007**	**11**	**.76**	**.007**
$(D_2 \times D_3 \times 5\text{-}HT_7)/5\text{-}HT_{1A}$			$D_2(5\text{-}HT_{2A} \times 5\text{-}HT_{2C} \times 5\text{-}HT_7)/5\text{-}HT_{1A}$			$D_3(5\text{-}HT_{2A} \times 5\text{-}HT_{2C} \times 5\text{-}HT_7)/5\text{-}HT_{1A}$			$(D_2 \times D_3 \times 5\text{-}HT_{2A} \times 5\text{-}HT_{2C})/5\text{-}HT_{1A}$		
n	*r*	p value	n	*r*	p value	n	*r*	p value	n	*r*	p value
11	**.74**	**.010**	**11**	**.62**	**.042**	**11**	**.65**	**.031**	**11**	**.72**	**.013**

Bold font indicates p-value < 0.05

follow the approach of the original analyses by Seeman and Creese demonstrating a linear correlation between a drug's binding affinity to D_2-family dopamine receptors and clinically effective antipsychotic drug dose [1, 2]. The assessment of binding data from cloned human dopamine and serotonin receptor subtypes provides an opportunity to test correlations between clinically effective drug dosages and affinity to catecholamine receptor subtypes which were not available for binding analyses at the time of these original studies in the 1970s. Here we include data from four additional atypical antipsychotic medications more recently approved by the United States Food and Drug Administration for efficacy targeting psychotic symptoms in schizophrenia. The increased sample size adds statistical power to identify significant relationships between antipsychotic effects of atypical antipsychotic medications and receptor binding targets. The major findings identified by these analyses are discussed below.

2.4.1 D3 Dopamine Receptor Provides a Molecular Binding Target for Antipsychotic Efficacy

Compared to earlier analyses, the addition of four new atypical antipsychotic medications to the data set increased the strength of correlation between D_3 dopamine receptor binding affinity and antipsychotic drug dose ($r = 0.77$, $p = 0.005$). The modest correlation between D_2 dopamine receptor binding affinity and atypical antipsychotic medication dose ($r = 0.59$, $p = 0.059$) is also strengthened in the current analysis, and is comparable in magnitude to the correlation between these measures for typical antipsychotic medications identified in our earlier study [($r = 0.54$, $p = 0.046$) [6]]. The earliest reports describing D_3 dopamine receptor expression suggested a role for this receptor as a molecular target for antipsychotic medications based upon the highly restricted pattern of D_3 receptor expression within limbic brain regions believed to play an important role in psychotic symptoms [25, 26]. D_3 dopamine receptor is believed to have primarily extrasynaptic localization, based

Table 2.6 Correlation between clinically effective antipsychotic dose and receptor binding affinity ratios

$5\text{-HT}_{2A} \times D_2$			$5\text{-HT}_{2C} \times D_2$			$5\text{-HT}_{2A} \times D_3$			$5\text{-HT}_{2C} \times D_3$			$D_2(5\text{-HT}_{1A}/5\text{-HT}_{2A})$			$D_2(5\text{-HT}_{1A}/5\text{-HT}_{2C})$		
n	*r*	p value	n	*r*	p value	n	*r*	p value	n	*r*	p value	n	*r*	p value	n	*r*	p value
11	**.62**	**.042**	11	.59	.057	**11**	**.71**	**.014**	**11**	**.65**	**.029**	11	.0024	.99	11	.098	.77
$5\text{-HT}_7 \times D_2$			$5\text{-HT}_7 \times D_3$			$D_2/5\text{-HT}_7$			$D_3/5\text{-HT}_7$			$D_3(5\text{-HT}_{1A}/5\text{-HT}_{2A})$			$D_3(5\text{-HT}_{1A}/5\text{-HT}_{2C})$		
n	*r*	p value	n	*r*	p value	n	*r*	p value	n	*r*	p value	n	*r*	p value	n	*r*	p value
11	.48	.16	11	.58	.06	11	.45	.16	11	.52	.10	11	.039	.91	11	.15	.65

Bold font indicates p-value < 0.05

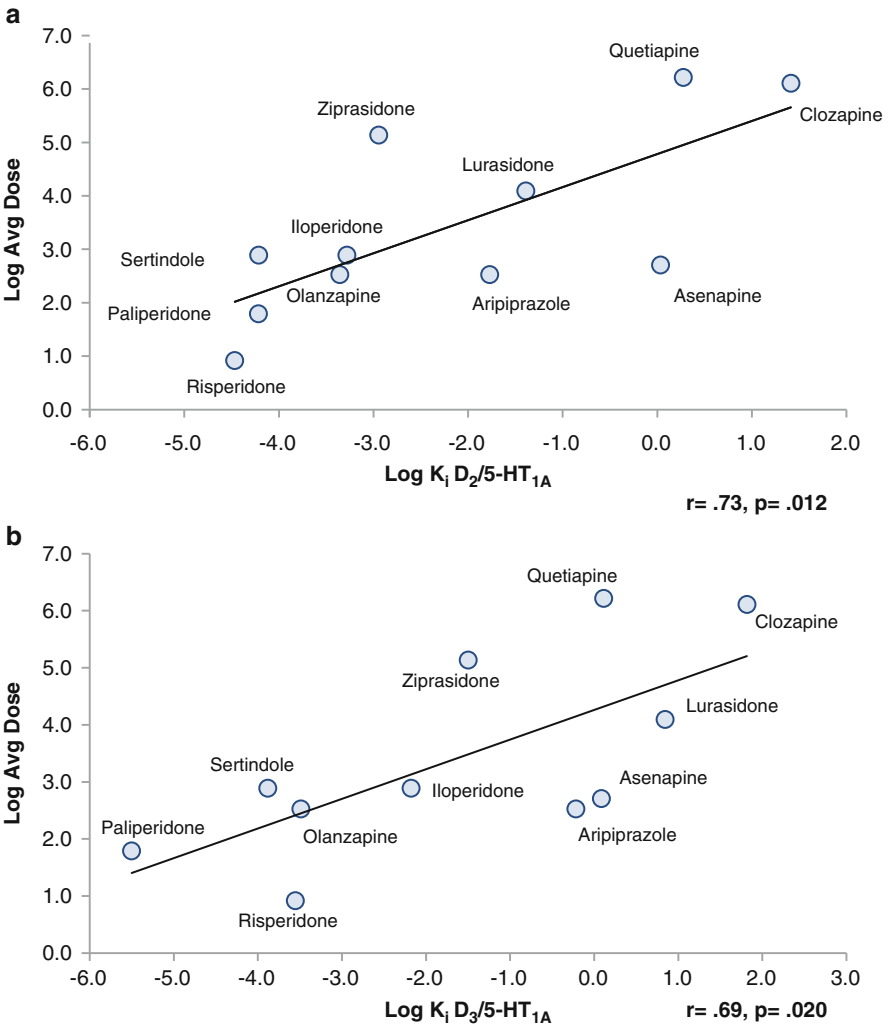

Fig. 2.3 Clinically effective antipsychotic medication dose vs. ratio of binding affinities to cloned human dopamine D_2/serotonin 5-HT_{1A} receptor (*upper panel*) and dopamine D_3/serotonin 5-HT_{1A} receptor (*lower panel*)

upon the lack of overlap between D_3 receptor protein expression and synaptic proteins such as synaptophysin [27]. Further evidence for a functional role sampling extra-synaptic dopamine concentrations comes from the high affinity of the D_3 receptor for dopamine. The low affinity state D_3 receptor Ki = 30 nM [26], close to basal extracellular dopamine concentrations (3–5 nM [28, 29]). In contrast, D_1 and D_2 receptor affinity for dopamine are far lower: D_2 K_i [(nM)] = 2,000, and D_1 K_i [(nM)] = 2,300 [26]. These differences in dopamine binding affinity are consistent

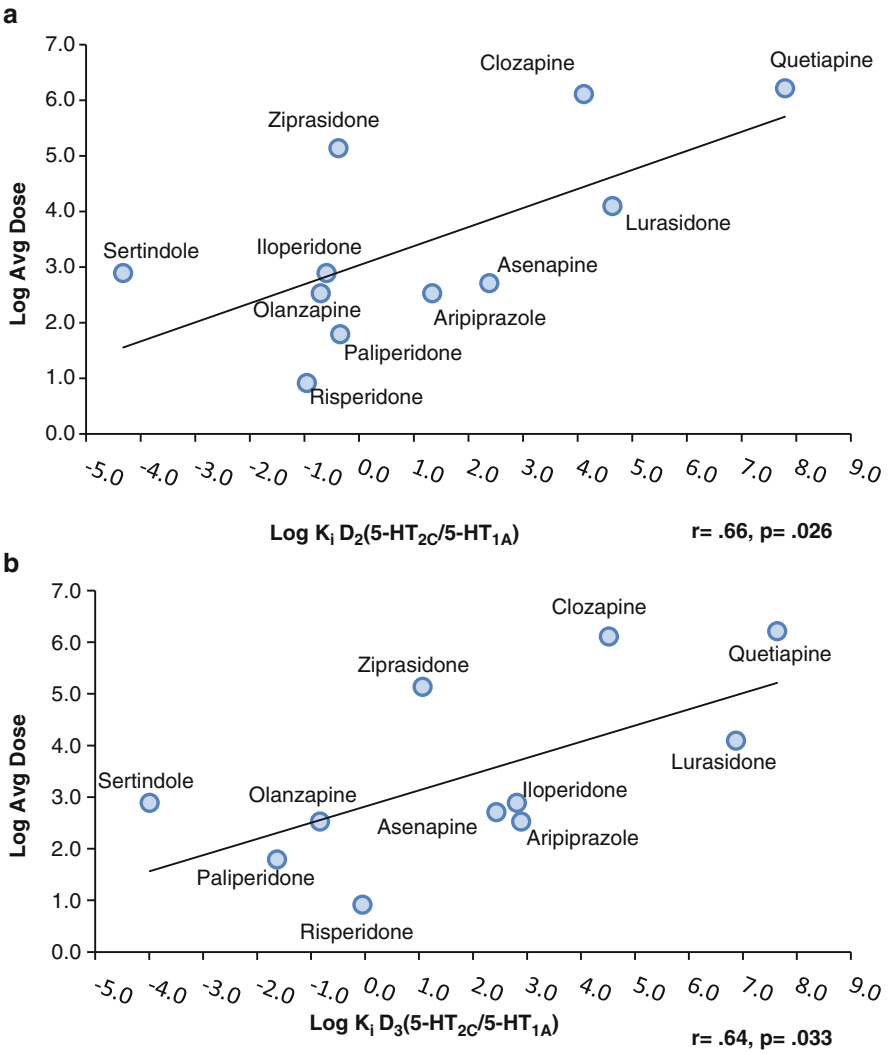

Fig. 2.4 Clinically effective antipsychotic medication dose vs. ratio of binding affinities to cloned human dopamine D_2 × (serotonin 5 -HT_{2C}/serotonin 5-HT_{1A}) receptor (*upper panel*) and dopamine D_3 × (serotonin 5 -HT_{2C}/serotonin 5-HT_{1A}) receptor (*lower panel*)

with the cellular localization of the D_3 receptor, suggesting D_3 receptor stimulation signals tonic dopamine concentrations, while post-synaptic D_1/D_2 receptor stimulation signals phasic dopamine concentrations.

Direct clinical evidence for D_3 receptor as a molecular target for effective treatment of psychotic symptoms of schizophrenia is more limited and variable. The D_3 receptor antagonist (+)-UH232 further worsened positive psychotic symptoms in schizophrenia patients following a single treatment dose. Patients receiving (+)-UH232

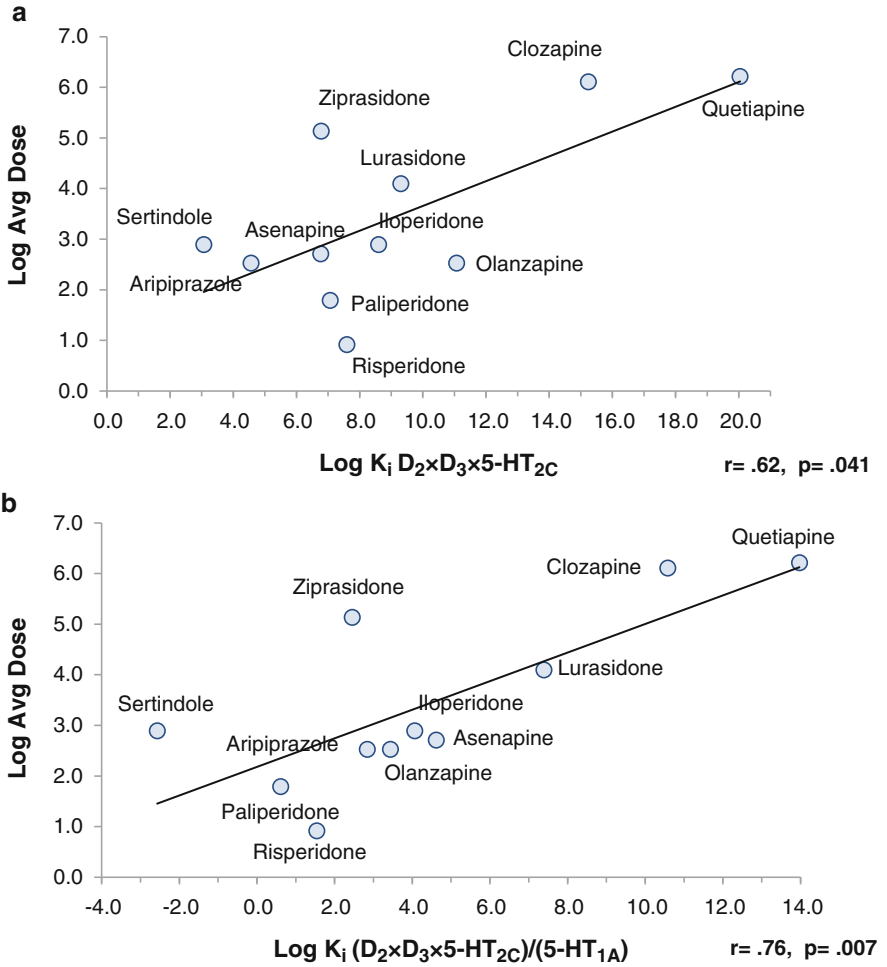

Fig. 2.5 Clinically effective antipsychotic medication dose vs. ratio of binding affinities to cloned human dopamine $D_2 \times D_3 \times$ serotonin 5 -HT_{2C} receptor (*upper panel*) and dopamine $D_2 \times D_3 \times$ serotonin 5 -HT_{2C}/serotonin 5-HT_{1A} receptor (*lower panel*)

in a placebo-controlled study experienced worsening of symptoms including unusual thought content, anxiety, activation, and hostility during the 8 h following single dose treatment [30]. In contrast, the partial D_3 dopamine receptor agonist (-)-3-(3-hydroxyphenyl)-N-n-propylpiperidine [(-)-3PPP] improved psychotic symptoms in schizophrenia patients for up to 1 week. The therapeutic benefit did not persist with repeated treatment in this study [31]. Because [(-)-3PPP] is a non-selective partial agonist with intrinsic activity at D_4 (83 %) and D_2 (35 %) as well as at D_3 (44 %) dopamine receptors [31], a specific role targeting D_3 dopamine receptor cannot be clearly determined from these observations. In a similar fashion, the

D_3 preferring agonist pramipexole exhibits approximately seven-fold greater potency at human D_3 relative to human D_2 receptor [32]. The addition of pramipexole to treatment with haloperidol improved symptoms in 60 % of schizophrenia patients [33]. Studies utilizing medications with higher D_3 receptor selectivity [34] would be needed to determine if psychotic symptoms in schizophrenia are effectively treated by monotherapy targeting the D_3 dopamine receptor in isolation, or if effective intervention requires coordinated effects simultaneously targeting multiple receptors in concert.

2.4.2 Serotonin Receptor Contributions to Antipsychotic Efficacy

Based upon preclinical studies examining effects of selective serotonin 5-HT_7 antagonists in animal models of relevance to psychotic and cognitive symptoms of schizophrenia [8–11], there has been considerable recent interest in potential therapeutic effects of serotonin 5-HT_7 antagonists in schizophrenia [7]. Our data analyses do not identify direct correlations between atypical antipsychotic medication dose and binding affinity to 5-HT_{1A}, 5-HT_{2A}, 5-HT_{2C}, or 5-HT_7 subtype serotonin receptors (Table 2.3). Therapeutic efficacy for atypical antipsychotic medications has been suggested to result from a balance of inhibition at dopamine D_2, serotonin 5-HT_{2A}, and 5-HT_{2C} receptors [18–21], while serotonin 5-HT_{1A} receptor stimulation appears to contribute to antipsychotic efficacy in rat models [23, 24, 35]. Consistent with these concepts and similar to our earlier analyses [6], the addition of four new atypical antipsychotic medications to the data set suggest therapeutic actions of atypical antipsychotic medications are impacted by combined binding effects at different receptor subtypes. Clinically effective dosages of atypical antipsychotic medication are highly correlated with the ratios of D_2/5-HT_{1A}, D_3/5-HT_{1A}, $D_3 \times$ 5-HT_{2A}, $D_2 \times$ 5-HT_{2A}, ($D_2 \times D_3 \times$ 5-HT_7)/5-HT_{1A}, ($D_2 \times D_3 \times$ 5-HT_{2A})/5-HT_{1A}, and ($D_2 \times D_3 \times$ 5-HT_{2C})/5-HT_{1A} receptor binding affinities. Thus, therapeutic potency of atypical antipsychotic medications is influenced by interactions among the following different domains: (1) Increasing D_3 and D_2 dopamine receptor binding affinity enhances antipsychotic potency. (2) Increasing serotonin 5-HT_{2A}, 5-HT_{2C}, and 5-HT_7 receptor binding affinities also facilitate antipsychotic efficacy. (3) Increasing 5-HT_{1A} receptor binding affinity, in contrast, reduces antipsychotic efficacy.

2.5 Limitations

Our analyses are limited to antipsychotic medication effects on positive psychotic symptoms, and do not address efficacy for negative symptoms or cognition which may be more important in terms of long-term functional outcome. Importantly, the strength of correlations between receptor binding and antipsychotic efficacy

identified in our analyses are restricted by a wide range of limiting factors. Medication differences in absorption; metabolism; protein binding; and the presence of pharmacologically active metabolites all serve to weaken the observed correlations. Additionally, the antipsychotic medication dose prescribed to patients may be determined in part by side effects, and might therefore not accurately reflect the "ideal" efficacy dose. The limited number of adequately powered clinical trials to determine optimal dose for antipsychotic medications further limits the accuracy of medication dosages employed in our analyses. Also, the binding data used in our analyses, measuring ligand binding to cloned human receptors expressed in cell culture systems, may be distinct from binding to limbic neurotransmitter receptor populations *in vivo*. Differences in receptor phosphorylation, glycosylation, and/or dimerization to hetero-oligomers [36–39] between in vivo and cell culture systems lacking post-translational machinery could potentially alter receptor binding affinity. And finally, this correlational approach is inherently limited by the complexities of brain circuitry in which dopamine and serotonin receptors may function as a "brake" in one brain region, and simultaneously as an "accelerator" in a different brain region. For example, blockade of D_2 dopamine autoreceptors in cell body regions of the ventral tegmentum increases both synthesis and release of dopamine, which could worsen psychotic symptoms, while blockade of postsynaptic D_2 receptors in limbic terminal regions would likely have an opposite behavioral effect. Thus, the dysfunction of schizophrenia, resulting from a complex interaction of multiple receptor and neurotransmitter systems [40], does not lend itself ideally to an analysis of isolated receptor systems.

2.6 Conclusions and Future Directions

In summary, the data presented above demonstrate correlations between clinically effective atypical antipsychotic medication dose and binding affinities to D_2, D_3, D_4, 5-HT_{1A}, 5-HT_{2A}, 5-HT_{2C} and 5-HT_7 receptor subtypes. Given the numerous limitations inherent in this approach (listed above), the strength of correlations described in these analyses suggest the dopamine and serotonin receptor subtypes analyzed provide the preponderance of antipsychotic effect of these medications. The specific mechanism(s) underlying this clinical effect, however, remains obscure. The "disconnect" between the pharmacokinetics of receptor blockade and the extended time lag until clinical benefit suggest antipsychotic efficacy, while initiated through binding to neurotransmitter receptor target(s), is likely the consequence of a downstream cascade of alterations in gene transcription and translation. Studies identifying the specific targets of altered gene transcription resulting from these drug-neurotransmitter receptor interactions would therefore have high likelihood of improving specificity and efficacy of antipsychotic medications.

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