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Neuroreceptor imaging in psychiatric disorders

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Molecular imaging, the study of receptors, transporters and enzymes, as well as other cellular processes, has grown in recent years to be one of the most active neuroimaging areas. The application of single photon emission tomography (SPECT) and positron emission tomography (PET) techniques to the study of psychiatric illness has lead to increased understanding of disease processes as well as validated, *in vivo*, theories of illness etiology. Within the field of psychiatry these techniques have been applied most widely to the study of schizophrenia. Studies within schizophrenia are largely limited to either the dopamine or serotonin system. This is due in large part to the availability of suitable radiotracers as well as the current theories on the etiology of the illness. Two basic study designs are used when studying schizophrenia using molecular imaging and make up the majority of studies reviewed in this manuscript. The first type, termed "clinical studies," compares the findings from PET and SPECT studies in those with schizophrenia to normal controls in an attempt to understand the pathophysiology of the illness. The second study design, termed "occupancy studies," uses these techniques to enhance the understanding of the mechanism of action of the medications used in treating this lllness. This review will focus on the findings of molecular imaging studies in schizophrenia, focusing, for the most part, on the serotonin and dopamine systems. Emphasis will be placed on how these findings and techniques are currently being used to inform the development of novel treatments for schizophrenia.

Key words: PET, SPECT, schizophrenia, dopamine, serotonin

INTRODUCTION

OVER THE PAST 10 to 15 years technological advances have allowed for the application of new techniques to the study of psychiatric disorders. Specifically there has been a dramatic escalation in the number of studies employing single photon emission tomography (SPECT) or positron emission tomography (PET) to study the neuroreceptors implicated in various psychiatric disorders. For the most part early PET studies of flow and metabolism using [^{15}O]H_2O and [^{18}F]fluorodeoxyglucose ([^{18}F]FDG) have largely been replaced by fMRI, which offers clear advantages in terms of spatial and temporal resolution, not to mention the lack of radiation exposure. In contrast, the ability of PET and SPECT to image specific biomolecules is unmatched by any other method currently available to clinical investigators. Studies of receptors, transporters, enzymes and other processes such as transmitter synthesis and release (a set of techniques referred to as molecular imaging) constitute the most distinctive application of PET/SPECT for current and future psychiatric research.

The majority of PET and SPECT studies in psychiatry have focused on the illness of schizophrenia and, although there are exceptions, most studies focus on one of two neurotransmitter systems, either the serotonin system or the dopamine system. This is due, in large part, to the radiotracers available for use and to current theories on the etiology of schizophrenia. The aim of this manuscript is to review the major findings stemming from the application of molecular imaging techniques to the study of schizophrenia with an emphasis on how these techniques are being used to inform the development of novel treatments.

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Two basic paradigms are used in the studies reviewed here. The first type of study (termed "clinical studies") investigates a specific biomolecular process in psychiatric patients and normal controls, in an effort to understand the neurochemical imbalances associated with the pathophysiology of the condition under study. The second type of investigation (termed "occupancy studies") uses molecular imaging techniques to improve our understanding of the mechanism of action of psychiatric medications. Both types of studies have revealed important information about psychiatric disorders and their treatment.

DOPAMINE

The neurotransmitter system most extensively studied with PET/SPECT is the dopamine system. This likely relates to both the availability of suitable radioligands and the fact that an alteration in dopamine transmission has been proposed in schizophrenia for over 30 years.[1,2] A hyperactivity of the dopamine system was postulated based on the observation that all effective antipsychotic medications display some degree of blockade at the D_2 receptor, a statement which holds true today.[3,4] PET and SPECT imaging have been used to study dopamine receptors in two brain regions, the cortex and the striatum. We will first discuss studies which focus on striatal dopamine receptors since these studies are more numerous as radioligands suitable for imaging cortical dopamine receptors have only recently been developed.

1) Striatal Dopamine

The D_2 receptor is the most numerous dopamine receptor in the striatum. Both clinical and occupancy studies have been performed using PET and SPECT techniques with a variety of radiotracers. These radiotracers include butyrophenones ([^{11}C]*N*-methylspiperone, [^{11}C]NMSP, and [^{76}Br]bromospiperone), benzamides ([^{11}C]raclopride, and [^{123}I]IBZM), and the ergot derivative, [^{76}Br]lisuride. In addition to providing valuable information about a variety of psychiatric illnesses these studies have allowed investigators to test the dopamine hypothesis of schizophrenia in the living human brain.

(1) Clinical Studies

A recent meta-analysis[5] identified 17 imaging studies comparing D_2 receptor parameters in patients with schizophrenia (a total of 245 patients, 112 neuroleptic naive and 133 neuroleptic free) and controls (n = 231), matched for age and sex.[6–22] Two out of 17 studies detected a significant elevation of D_2 receptor density parameters in patients with schizophrenia. A small (12%), but significant, elevation of striatal D_2 receptors was seen in the meta-analysis in patients with schizophrenia. Interestingly, the effect sizes were different for different classes of radiotracers. Studies performed with butyrophenones (n = 7) show an effect size of 0.96 ± 1.05, significantly larger than the effect size observed with other ligands (benzamides and lisuride, n = 10, 0.20 ± 0.26, p = 0.04). This difference might be due to differences in vulnerability of the binding of these tracers to competition by endogenous DA, and elevation of endogenous DA in schizophrenia.[23,24]

Fewer studies have looked at striatal D_1 receptors in schizophrenia. The three imaging studies[12,25,26] which have confirmed the results of postmortem studies demonstrating unaltered levels of these receptors compared to controls.

More recently studies have used the property of competition at the receptor between dopamine radioligands and endogenous dopamine to assess for differences in dopamine transmission in disease states compared with controls and non-ill states. These studies generally use pharmacological methods to manipulate the release of dopamine thereby allowing for a direct evaluation of dopamine activity. Two specific pharmacological paradigms have been used; the first utilizes amphetamine stimulated dopamine release to assess presynaptic neuronal activity. The second uses the drug alpha-methyl-para-tyrosine (AMPT) which inhibits dopamine synthesis and thereby allows for the determination of endogenous dopamine levels prior to depletion with AMPT.

Amphetamine-induced DA release. Numerous groups have demonstrated that an acute increase in synaptic DA concentration is associated with decreased *in vivo* binding of [^{11}C]raclopride and [^{123}I]IBZM (for review of this abundant literature, see[27]).

Compared to controls, the amphetamine-induced decrease in [^{11}C]raclopride or [^{123}I]IBZM binding is elevated in untreated patients with schizophrenia.[16,18,19] In addition, the magnitude of DA release was significantly related to a transient induction of symptoms by amphetamine. This increased DA release was unrelated to previous medication treatment and was observed in both first episode/drug naive patients and previously treated patients.[28] Another important finding was that this elevated release of dopamine in response to amphetamine was seen only during illness exacerbation and not in subjects who were in remission.[28]

Although the most common interpretation of these findings is that schizophrenic subjects show an increased release of dopamine in response to amphetamine, another interpretation would be that schizophrenia is associated with increased affinity of D_2 receptors for DA. Development of D_2 receptor imaging with radiolabeled agonists is needed to settle this issue.[29]

Endogenous dopamine levels. A limitation of the amphetamine challenge imaging studies is that they measure changes in synaptic DA transmission following a non-physiological challenge (i.e. amphetamine) and do not provide any information about synaptic DA levels at baseline, i.e. in the unchallenged state. Several laboratories have reported that, in rodents, acute depletion of synaptic DA is associated with an acute increase in the *in*

vivo binding of [^{11}C]raclopride or [^{123}I]IBZM to D_2 receptors (for review, see[27]). The increased binding is observed *in vivo* but not *in vitro*, indicating that it is not due to receptor upregulation,[30] but to removal of endogenous DA and unmasking of D_2 receptors previously occupied by DA. The acute DA depletion technique was developed in humans using AMPT, to assess the degree of occupancy of D_2 receptors by DA.[30,31] Using this technique, higher occupancy of D_2 receptors by DA has been reported in patients with schizophrenia experiencing an episode of illness exacerbation, compared to healthy controls.[20] Again, assuming normal affinity of D_2 receptors for DA, the data are consistent with higher DA synaptic levels in patients with schizophrenia. Increased D_2 receptor stimulation by DA at the time of admission (measured with the AMPT paradigm) was found to be predictive of a rapid clinical response to antipsychotic drugs,[20] a finding that illustrates the potential of PET or SPECT molecular imaging to predict treatment response.

The results of studies looking as both endogenous dopamine and amphetamine stimulated dopamine release provide direct evidence of the dopamine hypothesis of schizophrenia. In the future, the use of PET cameras with improved resolutions will allow investigators to examine differences in dopamine function between the ventral (limbic) and dorsal (motor) striatum. Unanswered questions remain regarding dopamine function in schizophrenia in important extrastraital regions such as the amygdala, hippocampus and cingulate cortex. Radiotracers currently in use or in development such as [^{11}C]FLB[32] and [^{11}C]fallypride[33] can be used to image the D_2 receptor in these extrastriatal regions and may serve to expand the understanding of the dopamine abnormalities in schizophrenia.

Other measures of dopamine function in the stratum have been examined by molecular imaging techniques. These include studies which have used [^{18}F] or [^{11}C]DOPA to assess the activity of DOPA decarboxylase. Five studies[34–38] have used this method, four of these report an increase in striatal DOPA in schizophrenic subjects. This provides further support for an increase in dopamine synthesis activity in schizophrenia, although it must be kept in mind that DOPA decarboxylase is not the rate limiting enzyme in dopamine synthesis.

The elevated striatal dopamine seen in schizophrenia could be due to an increase in the density of dopamine nerve terminals compared to controls. This questions has been examined by different groups using radioligands to assess the dopamine transporter (DAT). The DAT resides exclusively on dopamine nerve terminals in the striatum and has been used as a marker of dopamine innervation.[39] No differences in DAT binding of [^{123}I]β-CIT[40], [^{18}F]CFT[41] or [^{123}I]FP-CIT[42] were seen in schizophrenic subjects compared to controls indicating that the striatal dopamine abnormalities of schizophrenia are not due to increased dopamine innervation.

(2) Occupancy Studies

Occupancy of striatal D_2 receptors by antipsychotic medications is a major area of research in psychiatry, specifically as it relates to the treatment of schizophrenia. An example of how these studies have provided new insights into the treatment of this illness can be found in studies which compare the receptor occupancy of typical antipsychotic medications (i.e. haloperidol) with that of the newer antipsychotic agents (i.e. risperidone, olanzapine, quetiapine, ziprasidone and clozpapine).

A number of SPECT and PET studies using various radioligands demonstrate that clozapine has lower D_2 receptor occupancy than the typical antipsychotics (see 14–16 in[43] and 2, 9, 12, 17, 18, 21, 25, 26 in[44]). For example, Tauscher et al,[45] using [^{123}I] IBZM SPECT imaging found mean D_2 receptor occupancy of 33% for patients on clozapine at doses of 300 to 600 mg/day, compared to 84% for patients on haloperidol in doses of 5 to 20 mg/day. Of course, this method only estimates binding to striatal receptors and begs the question whether these are equivalent dose ranges. Using the same technique (i.e. IBZM SPECT), Pickar et al.[44] showed a wide range (18–80%) of D_2 occupancy among 13 patients treated with clozapine (mean 510 mg/day S.D. = 184). All of these occupancy values were associated with favorable response to clozapine. Using [^{11}C]raclopride PET imaging, Farde et al.[46] showed D_2 receptor occupancy between 70 and 89% in 22 patients on conventional agents, compared to 38 to 63% in five patients on clozapine. These authors contend that dosing does not account for the difference as clozapine was administered in the "higher clinical range" and the conventional drugs in the "low to moderate range." In another PET study[47] D_2 receptor occupancy for clozapine ranged from 20 to 67%, also lower than conventional antipsychotics. Also using [^{11}C] raclopride imaging, Kapur et al. showed that adding haloperidol to clozapine increased D_2 receptor occupancy in five patients from a mean of 55% to 79%. These investigators have advanced the notion that there is a threshold for clinical response to antipsychotic drugs that occurs at about 60% receptor occupancy and that EPS and hyperprolactinemia require occupancy above 80%.[48] Although these "thresholds" are not universally agreed upon, there is general consensus that, at least insofar as the striatum is concerned, clozapine has lower D_2 receptor occupancy in the clinical dosing range than conventional drugs.

There is less agreement on whether other atypical medications have lower striatal D_2 affinity or whether occupancy differences are dose-related. Kapur et al.,[49] using [^{11}C]raclopride PET, found D_2 occupancy for olanzapine between 43 and 80% for patients taking 5–20 mg/day and 83 to 88% for patients taking 30–40 mg/day. With IBZM SPECT, Lavalaye et al.[50] found D_2 occupancy for olanzapine of 62% in a group of patients taking 15 mg/day. At a mean dose of 18 mg/day, Tauscher et al.[45]

found a mean D_2 receptor occupancy for olanzapine of 75%. Nordstrom et al. also found high D_2 receptor occupancy for olanzapine in a PET study.[51] D_2 receptor occupancy appears to be dose-related for olanzapine.[49,52,53]

Similar degrees of D_2 receptor occupancy have been found for risperidone at therapeutic doses. For example, Remington et al.[54] in a raclopride PET study found a range of D_2 occupancies as follows: 66% on 2 mg/day, 73% on 4 mg/day, and 79% on 6 mg/day. Nyberg et al. reported that risperidone has similar potency to bind to D_2 receptors as haloperidol.[55] Others have also found relatively high D_2 receptor occupancy for risperidone.[56] Occupancy of D_2 receptors by risperidone was not significantly different from olanzapine in the Lavalaye et al. study,[50] although it was higher in the group taking 4 mg/day of risperidone (79%) than in the group taking 15 mg/day of olanzapine (62%). Because higher doses of risperidone and olanzapine appear to occupy numbers of D_2 receptors similar to typical agents and also are capable of producing EPS and prolactin increases, it is not clear if the lower D_2 receptor occupancy of these two agents is more a function of dose rather than lower affinity.

Quetiapine may be more like clozapine, remaining at low levels of D_2 receptor occupancy even at high doses. For example, Gefvert et al.[57] titrated patients to 450 or 750 mg/day of quetiapine and found D_2 occupancy of 30 and 41%, respectively. Kufferle et al. found D_2 occupancy of 30% for quetiapine at effective doses.[58] Kapur et al.[59] contend that quetiapine does produce high levels of D_2 receptor occupancy (58 to 64%), but that this lasts for only a few hours.

There are limited imaging data available of this sort for other atypicals, such as ziprasidone and aripiprazole. Taken together, however, while it is clear that clozapine and possibly quetiapine do not occupy as many striatal D_2 receptors as conventional antipsychotics, it is not obvious that this confers on atypical antipsychotics any unique therapeutic property other than the reduced risk for EPS and hyperprolactinemia. Kapur et al. have argued that low D_2 occupancy is not the important feature, but rather what distinguishes the atypical antipsychotic drugs is more rapid dissociation from the receptor.[60] This view is controversial, however.

Although much work has already been done in this area, more data are needed for the newer atypical drugs including ziprasidone, iloperidone, and aripiprazole. However, it is very plausible that measuring D_2 binding in striatum, a limitation of the currently available IBZM and PET radioligands, will not yield a distinguishing feature of atypical antipsychotics. The development of radiotracers which allow for imaging the D_2 receptors in brain regions outside of the striatum may help clarify this issue.

2) Cortical Dopamine

The role of dopamine in the prefrontal cortex (PFC), particularly in schizophrenia, is an area of intensive investigation. It has been suggested that deficiencies in dopamine function in this area result in the cognitive impairments and the negative symptoms of the illness.[61–63] The majority of DA receptors in the PFC are of the D_1 subtype.[64,65] Currently two PET radioligands are available to analyze the D_1 receptor, [^{11}C]SCH 23390 and [^{11}C]NNC 112. The results from studies utilizing these ligands in schizophrenia are contradictory. Okubo et al., using [^{11}C]SCH 23390, reported decreased density of PFC D_1 receptors in patients with schizophrenia.[12] This low PFC D_1 correlated with the degree of negative symptoms and poor performance on a test of prefrontal functions (the Wisconsin Card Sorting Test, WCTS). In contrast, a more recent study using [^{11}C]NNC 112 reported increased D_1 receptor availability in the dorsolateral PFC (DLPFC) of patients with sehizophrenia.[26] In this study the increase correlated with poor performance on a test of working memory (the n-back task). The reason for the discrepancy in the results obtained with [^{11}C]SCH 23390 and [^{11}C]NNC 112 remains to be elucidated, but it is interesting to note that the binding of both radiotracers is differentially affected by endogenous DA competition and receptor trafficking.[27] For example, chronic DA depletion in rodents is associated with decreased and increased *in vivo* binding of [^{11}C]SCH 23390 and [^{11}C]NNC 112, respectively.[26] Thus, the contradictory observations of decreased [^{11}C]SCH 23390 binding[12] and increased [^{11}C]NNC 112 binding[26] observed in the PFC in patients with schizophrenia may in fact both represent the consequences of a sustained deficit in prefrontal DA function.

SEROTONIN

The fact that LSD, a powerful hallucinogen, acts as both a serotonin agonist as well as antagonist lead to speculation that alterations in the serotonin system play a role in the pathogenesis of schizophrenia.[66] Postmortem studies have described abnormalities of the serotonin transporter (SERT), 5-HT_{2A} receptors and, more consistently, 5-HT_{1A} receptors (see references in[67]). Given the relatively recent development of radiotracers to study 5-HT receptors, only a limited number of imaging studies have been published.

1) Clinical Studies

Specific alterations in serotonin receptors seen in post mortem studies include a decrease in 5-HT_{2A} receptors in the PFC (4 out of 8 studies), an increase in the density of 5-HT_{1A} receptors in the PFC (7 out of 8 studies) and a reduction in the density of the SERT in the PFC (3 out of 4 studies).[67] *In vivo* imaging studies in this area are limited and often contradict the postmortem findings. For example, three PET studies in drug-naive or drug-free patients with schizophrenia have reported normal cortical 5-HT_{2A} receptor binding,[68–70] while one study has reported a significant decrease in PFC 5-HT_{2A} binding in a

small group (n = 6) of drug naive schizophrenic patients.[71] No *in vivo* PET studies have been published which look at the 5-HT_{1A} receptors in schizophrenia. Several groups are currently evaluating the binding of this receptor *in vivo* with PET using the radioligand [^{11}C]WAY100635.

There have not been any molecular imaging studies of the SERT density in the cortex. One study which looked at the concentration of SERT in the midbrain measured by [^{123}I]β-CIT found it to be unaltered in patients with schizophrenia.[40] However, studies with more specific SERT ligands are warranted to assess the distribution of SERT in other brain areas, such as the PFC, in order to complement the postmortem findings. The first PET radiotracer available to measure SERT in humans was [^{11}C]McN 5652.[72] The usefulness of [^{11}C]McN 5652 as a PET tracer for SERT was validated in primates[73] and humans.[74–76] Unfortunately, [^{11}C]McN 5652 has many limitations, which include high non-specific binding, poor signal to noise ratio, non-measurable free fraction in the plasma and slow clearance from the brain.[75] Therefore, studies using [^{11}C]McN 5652 require long scanning time (up to 120 min), and this ligand can provide reliable quantification of SERT only in regions of relatively high SERT density (midbrain, thalamus and striatum). More recently, compounds from the phenylamine class have emerged as promising targets for both SPECT and PET tracer development. [^{123}I]ADAM[77] is a highly selective SPECT imaging agent for SERT. Its C-11 labeled counterpart, [^{11}C]ADAM, was recently reported.[78] Another compound in this series, [^{11}C]DASB, was recently introduced and has been evaluated in rats[79] and humans.[80] Thus, it is anticipated that, in the near future, several studies will be performed to evaluate SERT density with PET in patients with schizophrenia.

2) Occupancy Studies

Meltzer et al. proposed that the 5-HT_2/D_2 ratio of pKi values differentiated atypical antipsychotic medications from typical antipsychotic medications.[81] This hypothesis led to the development of medications with increased 5-HT_{2a} antagonism relative to D_2 antagonism.[82] There is evidence that antagonism at the 5-HT_{2a} receptor plays a role in the antipsychotic effects as well as the cognitive improvement, reduced EPS and improvement in negative symptoms seen with the atypical medications.[82]

With regard to 5-HT_{2a} receptor binding a fair number of recent imaging studies have looked at the atypical antipsychotic medications. However, information on the binding of typical antipsychotic medications to the 5-HT_{2a} receptor in human subjects is very limited.

Given clozapine's high *in vitro* affinity for the 5-HT_{2a} receptor it is not surprising that occupancy of this receptor by clozapine is high even at low serum levels of this medication. Nordström et al. used the radiotracer [^{11}C]*N*-methylspiperone to image the 5-HT_{2a} receptor in five schizophrenic subjects on clozapine.[47] When compared to six neuroleptic naïve schizophrenic patients the 5-HT_{2a} occupancy ranged from 84–94%. Thus the receptor occupancy values were quite high despite the large range of clozapine serum levels at the time of the scan (120 ng/m*l* to 1060 ng/m*l*). Using a different radiotracer, [^{18}F]setoperone, Trichard and colleagues compared the 5-HT_{2a} receptor occupancy of clozapine (N = 4), chlorpromazine (N = 17) and amisulpride (N = 5).[83] For standard binding values they used fourteen untreated schizophrenic patients who had been off medications for at least five weeks. Those in the clozapine group displayed near 100% occupancy of the 5-HT_{2a} receptors whereas those taking chlorpromazine had a mean occupancy of 51%. The subjects who were receiving amisulpride, a selective D_2/D_3 antagonist, did not demonstrate any 5-HT_{2a} binding. A more recent study, also using [^{18}F]setoperone, measured 5-HT_{2a} receptor occupancy in 27 subjects: 7 on risperidone, 12 on olanzapine and 9 on clozapine.[84] When compared to age-corrected binding potentials for 11 medication free schizophrenic subjects and 26 normal controls, all subjects exhibited a high degree of 5-HT_{2a} occupancy. Despite a range of medication doses within each group only one subject had an occupancy level below 90% (72% on 2 mg/day of risperidone). Other studies have also revealed high levels of 5-HT_{2a} receptor occupancy for risperidone. Greater than 80% occupancy was reported in a small sample of seven subjects taking 3 mg/day of risperidone.[55] When these same subjects were taking a higher dose of risperidone (6 mg/day) the 5-HT_{2a} receptor occupancy was 95%.

Quetiapine also occupies the 5-HT_{2a} receptor in a dose dependent manner, although at lower levels than risperidone, olanzapine or clozapine. Two studies using different radiotracers, ([^{11}C]*N*-methylspiperone and [^{18}F]setoperone), revealed consistent results.[57,59] The occupancy level ofthe 5-HT_{2a} receptor ranged from 19–94% over a dose range of 150 to 600 mg/day of quetiapine. These studies indicate that quetiapine, like the other atypicals, has the ability to saturate the 5-HT_{2a} receptor, although only at the upper end of the clinical dose range.

One of the few PET studies to look at 5-HT_{2a} binding by a typical antipsychotic used the radiotracers [^{18}F]setoperone and [^{11}C]raclopride to assess D_2 occupancy in 10 subjects taking loxapine.[85] Although *in vitro* studies have suggested that loxapine has a higher binding affinity for the 5-HT_{2a} receptor than the D_2 receptor[81,86] this clinical study found nearly equivalent occupancy of these two receptors. This highlights the difficulty of generalizing the results of preclinical studies to clinical effects.

The imaging studies mentioned above support the hypothesis that 5-HT_{2a} receptor antagonism is an important feature of atypical antipsychotics and, in fact, may be the defining feature of this class of medications. The mechanism by which 5-HT_{2a} blockade translates into improvements in clinical functioning remains an area of

active study. Several lines of evidence exist to explain why antagonism at this receptor may be beneficial in schizophrenia, including differential modulation of dopamine release in prefrontal and subcortical brain regions, effects on glutamate transmission as well as enhancement of cholinergic functioning (for reviews, see[87–90]). Much of the data supporting the various hypothesis regarding the role of 5-HT_{2a} antagonism have been generated from preclinical work including *in vitro*, rodent and nonhuman primate studies. Further advances in the field of brain imaging may allow testing of these hypotheses directly in clinical populations.

DRUG DEVELOPMENT AND FUTURE DIRECTIONS

There has been an increasing interest in and utilization of PET and SPECT imaging by pharmaceutical companies. These techniques are being used both to assess the *in vivo* properties of currently marketed drugs as well as to help with the development of new medications for psychiatric conditions.[91]

One particular area were this has been applied is in determining the appropriate dosage of medications. For example, the time lag (typically 1–2 weeks) in the onset of therapeutic effect of several classes of antidepressant medication may be related to the need for downregulation of 5-HT_{1A} somatodendritic autoreceptors in the raphe before a net increase in forebrain 5-HT neurotransmission can occur.[92] Because of this phenomenon, several groups have investigated whether the concomitant use of pindolol (antagonist at 5-HT_{1A} receptor and β-adrenoceptor) with an SSRI antidepressant might accelerate the onset of an improvement in mood. The results of clinical trials were inconsistent (for reviews, see[93,94]). Most clinical studies have used a dose of 7.5 mg daily of pindolol. Several PET centers have recently conducted human occupancy studies of pindolol at the postsynaptic and somatodendritic 5-HT_{1A} receptor.[95–97] The consensus from these studies is that the dose used in clinical studies was too low to provide appropriate and reliable blockade of 5-HT_{1A} receptors and that this factor might explain the limited success of this strategy in previous clinical trials.

The occupancy studies described in the previous sections provide examples of how molecular imaging can be used to better understand the clinical dosing of a particular medication. For example, the maximum dose of a medication may have been established in the Phase III trials by the appearance of unwanted side effects at levels above that dose. It may be of interest to the pharmaceutical company manufacturing the compound whether this maximum dose achieves a particular level of occupancy at the intended neuroreceptors. *In vivo* molecular imaging studies are particularly suited to answer this type of question.

These studies provide an illustration of the potential of PET neuroreceptor imaging to facilitate the use of currently approved medications. Other examples exist in which PET neuroreceptor imaging is being used to facilitate new drug development. In our group we are currently involved in an industry sponsored phase II trial examining the D_2 receptor occupancy of a new atypical antipsychotic formulation. The goal of the trial is to establish an appropriate dosing strategy (i.e. determining the doses at which less than 80% occupancy of the D_2 receptor is seen) for this formulation which can be used to inform the design of Phase III studies.

The application of molecular imaging techniques in psychiatry continues to develop. Many labs are actively working on the creation of new radiotracers to study neuroreceptor systems, such as the glutamate and GABA systems, which, as of yet, have not been explore by this method. Efforts are also being made to extend the reach of this technique beyond extracellular processes. For example, a recent study[98] demonstrated that it is possible to study intracellular response to receptor stimulation in nonhuman primates with PET. The application of this method to human studies would allow for the direct visualization of the intracellular response to medication treatment, opening up many new avenues of investigation.

REFERENCES

1. Rossum V. The significance of dopamine receptor blockade for the mechanism of action of neuroleptic drugs. *Arch Int Pharmacodyn Therapy* 1966; 160: 492–494.
2. Carlsson A, Lindqvist M. Effect of chlorpromazine or haloperidol on formation of 3-methoxytyramine and normetanephrine in mouse brain. *Acta Pharmacol Toxicol* 1963; 20: 140–144.
3. Creese I, Burt DR, Snyder SH. Dopamine receptor binding predicts clinical and pharmacological potencies of antischizophrenic drugs. *Science* 1976; 19: 481–483.
4. Seeman P, Chau-Wong M, Tedesco J, Wong K. Brain receptors for antipsychotic drugs and dopamine: direct binding assays. *Proc Natl Acad Sci USA* 1975; 72 (11): 4376–4380.
5. Weinberger DR, Laruelle M. Neurochemical and neuropharmacological imaging in schizophrenia. In: Davis KL, Charney DS, Coyle JT, Nemeroff C, editors. *neuropharmacology—The Fifth Generation of Progress*. Lippincott, Williams, and Wilkins, 2001.
6. Wong DF, Wagner HN, Tune LE, Dannals RF, Pearlson GD, Links JM, et al. Positron Emission Tomography reveals elevated D_2 dopamine receptors in drug-naive schizophrenics. *Science* 1986; 234: 1558–1563.
7. Crawley JC, Owens DG, Crow TJ, Poulter M, Johnstone EC, Smith T, et al. Dopamine D2 receptors in schizophrenia studied *in vivo*. *Lancet* 1986; 2 (8500): 224–225.
8. Blin J, Baron JC, Cambon H, Bonnet AM, Dubois B, Loc'h C, et al. Striatal dopamine D2 receptors in tardive dyskinesia: PET study. *J Neurol Neurosurg Psychiatry* 1989; 52 (11): 1248–1252.
9. Martinot J-L, Peron-Magnan P, Huret J-D, Mazoyer B, Baron J-C, Boulenger J-P, et al. Striatal D_2 dopaminergic

receptors assessed with positron emission tomography and ^{76}Br-bromospiperone in untreated patients. *Am J Psychiatry* 1990; 147: 346–350.
10. Tune LE, Wong DF, Pearlson G, Strauss M, Young T, Shaya EK, et al. Dopamine D2 receptor density estimates in schizophrenia: a positron emission tomography study with ^{11}C-*N*-methylspiperone. *Psychiatry Research* 1993; 49 (3): 219–237.
11. Nordstrom AL, Farde L, Eriksson L, Halldin C. No elevated D2 dopamine receptors in neuroleptic-naive schizophrenic patients revealed by positron emission tomography and [^{11}C]*N*-methylspiperone [see comments]. *Psychiatry Res* 1995; 61 (2): 67–83.
12. Okubo Y, Suhara T, Suzuki K, Kobayashi K, Inoue O, Terasaki O, et al. Decreased prefrontal dopamine D1 receptors in schizophrenia revealed by PET. *Nature* 1997; 385 (6617): 634–636.
13. Farde L, Wiesel F, Stone-Elander S, Halldin C, Nordsröm AL, Hall H, et al. D2 dopamine receptors in neuroleptic-naive schizophrenic patients. A positron emission tomography study with [^{11}C]raclopride. *Arch Gen Psychiatry* 1990; 47: 213–219.
14. Hietala J, Syvälahti E, Vuorio K, Nagren K, Lehikoinen P, Ruotsalainen U, et al. Striatal D2 receptor characteristics in neuroleptic-naive schizophrenic patients studied with Positron Emission Tomography. *Arch Gen Psychiatry* 1994; 51: 116–123.
15. Pilowsky LS, Costa DC, Ell PJ, Verhoeff NPLG, Murray RM, Kerwin RW. D2 dopamine receptor binding in the basal ganglia of antipsychotic-free schizophrenic patients. An I-123-IBZM single photon emission computerized tomography study. *Br J Psychiatry* 1994; 164: 16–26.
16. Laruelle M, Abi-Dargham A, van Dyck CH, Gil R, De Souza CD, Erdos J, et al. Single photon emission computerized tomography imaging of amphetamine-induced dopamine release in drug free schizophrenic subjects. *Proc Natl Acad Sci USA* 1996; 93: 9235–9240.
17. Knable MB, Egan MF, Heinz A, Gorey J, Lee KS, Coppola R, et al. Altered dopaminergic function and negative symptoms in drug-free patients with schizophrenia. [^{123}I]-iodobenzamide SPECT study. *Br J Psychiatry* 1997; 171: 574–577.
18. Breier A, Su TP, Saunders R, Carson RE, Kolachana BS, de Bartolomeis A, et al. Schizophrenia is associated with elevated amphetamine-induced synaptic dopamine concentrations: Evidence from a novel positron emission tomography method. *Proc Natl Acad Sci USA* 1997; 94 (6): 2569–2574.
19. Abi-Dargham A, Gil R, Krystal J, Baldwin R, Seibyl J, Bowers M, et al. Increased striatal dopamine transmission in schizophrenia: confirmation in a second cohort. *Am J Psychiatry* 1998; 155: 761–767.
20. Abi-Dargham A, Rodenhiser J, Printz D, Zea-Ponce Y, Gil R, Kegeles L, et al. Increased baseline occupancy of D2 receptors by dopamine in schizophrenia. *Proc Natl Acad Sci USA* 2000; 97 (14): 8104–8109.
21. Martinot JL, Paillère-Martinot ML, Loc'h C, Hardy P, Poirier MF, Mazoyer B, et al. The estimated density of D2 striatal receptors in schizophrenia. A study with positron Emission tomography and ^{76}Br-bromolisuride. *Br J Psychiatry* 1991; 158: 346–350.
22. Martinot JL, Paillère-Martinot ML, Loc'h C, Lecrubier Y, Dao-Castellana MH, Aubin F, et al. Central D2 receptors and negative symptoms of schizophrenia. *Br J Pharmacol* 1994; 164: 27–34.
23. Seeman P, Guan H-C, Niznik HB. Endogenous dopamine lowers the dopamine D_2 receptor density as measured by [^{3}H]raclopride: Implications for positron emission tomography of the human brain. *Synapse* 1989; 3: 96–97.
24. Seeman P. Brain dopamine receptors in schizophrenia: PET problems. *Arch Gen Psychiatry* 1988; 45: 598–560.
25. Karlsson P, Farde L, Halldin C, Sedvall G. D1-dopamine receptors in schizophrenia examined by PET. *Schizophrenia Res* 1997; 24: 179.
26. Abi-Dargham A, Gil R, Mawlawi O, Hwang DR, Kochan L, Lombardo I, et al. Selective alteration in D1 receptors in schizophrenia: a PET *in vivo* study. *J Nucl Med* 2001; 42: 17P.
27. Laruelle M. Imaging synaptic neurotransmission with *in vivo* binding competition techniques: a critical review. *J Cereb Blood Flow Metab* 2000; 20 (3): 423–451.
28. Laruelle M, Abi-Dargham A, Gil R, Kegeles L, Innis R. Increased dopamine transmission in schizophrenia: relationship to illness phases. *Biol Psychiatry* 1999; 46 (1): 56–72.
29. Hwang D, Kegeles LS, Laruelle M. (–)-*N*-[(11)C]propylnorapomorphine: a positron-labeled dopamine agonist for PET imaging of D(2) receptors. *Nucl Med Biol* 2000; 27 (6): 533–539.
30. Laruelle M, D'Souza CD, Baldwin RM, Abi-Dargham A, Kanes SJ, Fingado CL, et al. Imaging D-2 receptor occupancy by endogenous dopamine in humans. *Neuropsychopharmacology* 1997; 17 (3): 162–174.
31. Fujita M, Verhoeff NP, Varrone A, Zoghbi SS, Baldwin RM, Jatlow PA, et al. Imaging extrastriatal dopamine D(2) receptor occupancy by endogenous dopamine in healthy humans. *Eur J Pharmacol* 2000; 387 (2): 179–188.
32. Halldin C, Farde L, Hogberg T, Mohell N, Hall H, Suhara T, et al. Carbon-11-FLB 457: a radioligand for extrastriatal D2 dopamine receptors. *J Nucl Med* 1995; 36 (7): 1275–1281.
33. Mukherjee J, Yang ZY, Das MK, Brown T. Fluorinated benzamide neuroleptics—III. Development of (*S*)-*N*-[(1-allyl-2-pyrrolidinyl)methyl]-5-(3-[^{18}F]fluoropropyl)-2,3-dimethoxybenzamide as an improved dopamine D-2 receptor tracer. *Nucl Med Biol* 1995; 22 (3): 283–296.
34. Reith J, Benkelfat C, Sherwin A, Yasuhara Y, Kuwabara H, Andermann F, et al. Elevated dopa decarboxylase activity in living brain of patients with psychosis. *Proc Natl Acad Sci USA* 1994; 91: 11651–11654.
35. Hietala J, Syvalahti E, Vuorio K, Rakkolainen V, Bergman J, Haaparanta M, et al. Presynaptic dopamine function in striatum of neuroleptic-naive schizophrenic patients. *Lancet* 1995; 346 (8983): 1130–1131.
36. Hietala J, Syvalahti E, Vilknan H, Vuorio K, Rakkolainen V, Bergman J, et al. Depressive symptoms and presynaptic dopamine function in neuroleptic-naive schizophrenia. *Schizophrenia Res* 1999; 35 (1): 41–50.
37. Lindstrom LH, Gefvert O, Hagberg G, Lundberg T, Bergstrom M, Hartvig P, et al. Increased dopamine synthesis rate in medial prefrontal cortex and striatum in schizophrenia indicated by L-(beta-^{11}C) DOPA and PET. *Biol*

Psychiatry 1999; 46 (5): 681–688.
38. Dao-Castellana MH, Paillere-Martinot ML, Hantraye P, Attar-Levy D, Remy P, Crouzel C, et al. Presynaptic dopaminergic function in the striatum of schizophrenic patients. *Schizophrenia Res* 1997; 23 (2): 167–174.
39. Bannon MJ, Granneman JG, Kapatos G. *The dopamine transporter: potential involvement in neuropsychiatric disorders*. 1185 Ave of the Americas/New York/NY 10036; Raven Press, 1995.
40. Laruelle M, Abi-Dargham A, van Dyck C, Gil R, D'Souza DC, Krystal J, et al. Dopamine and serotonin transporters in patients with schizophrenia: an imaging study with [(123)I]beta-CIT. *Biol Psychiatry* 2000; 47 (5): 371–379.
41. Laakso A, Vilknan H, Alakare B, Haaparanta M, Bergman J, Solin O, et al. Striatal dopamine transporter binding in neuroleptic-naive patients with schizophrenia studied with positron emission tomography. *Am J Psychiatry* 2000; 157 (2): 269–271.
42. Lavalaye J, Linszen DH, Booij J, Dingemans PM, Reneman L, Habraken JB, et al. Dopamine transporter density in young patients with schizophrenia assessed with [^{123}I]FP-CIT SPECT. *Schizophr Res* 2001; 47 (1): 59–67.
43. Talvik M, Nordstrom A, Nyberg S, Olsson H, Halldin C, Farde L. No support for regional selectivity in clozapine-treated patients: A PET study with [^{11}C]Raclopride and [^{11}C]FLB 457. *Am J Psychiatry* 2001; 158: 926–930.
44. Pickar D, Su T, Weinberger D, Coppola R, Malhotra A, Knable M, et al. Individual variation in D2 dopamine receptor occupancy in clozapine-treated patients. *Am J Psychiatry* 1996; 153 (12): 1571–1578.
45. Tauscher J, Kufferle B, Asenbaum S, Fischer P, Pezawas L, Barnas C, et al. *In vivo* ^{123}I IBZM SPECT imaging of striatal dopamine-2 receptor occupancy in schizophrenic patients treated with olanzapine in comparison to clozapine and haloperidol. *Psychpharmacology* 1999; 141: 175–181.
46. Farde L, Nordstrom AL, Wiesel FA, Pauli S, Halldin C, Sedvall G. Positron emission tomographic analysis of central D1 and D2 dopamine receptor occupancy in patients treated with classical neuroleptics and clozapine. Relation to extrapyramidal side effects. *Arch Gen Psychiatry* 1992; 49 (7): 538–544.
47. Nordstrom AL, Farde L, Nyberg S, Karlsson P, Halldin C, Sedvall G. D1, D2, and 5-HT2 receptor occupancy in relation to clozapine serum concentration: a PET study of schizophrenic patients. *Am J Psychiatry* 1995; 152 (10): 1444–1449.
48. Remington G, Kapur S. D2 and 5-HT2 receptor effects of antipsychotics: Bridging basic clinical findings using PET. *J Clin Psychiatry* 1999; 60 (10): 15–19.
49. Kapur S, Zipursky R, Remington G, Jones C, DaSilva J, Wilson A, et al. 5-HT2 and D2 receptor occupancy of olanzapine in schizophrenia: A PET investigation. *Am J Psychiatry* 1998; 155 (7): 921–928.
50. Lavalaye J, Linszen D, Booij J, Reneman L, Gersons B, Royen E. Dopamine D2 receptor occupancy by olanzapine or risperidone in young patients with schizophrenia. *Psychiatric Research* 1999; 92: 33–44.
51. Nordstrom AL, Nyberg S, Olsson H, Farde L. Positron emission tomography finding of a high striatal D2 receptor occupancy in olanzapine-treated patients. *Arch Gen Psychiatry* 1998; 55 (3): 283–284.
52. Dresel S, Mager T, Rossmuller B, Meisenzahl E, Hahn K, Moller HJ, et al. *In vivo* effects of olanzapine on striatal dopamine D(2)/D(3) receptor binding in schizophrenic patients: an iodine-123 iodobenzamide single-photon emission tomography study. *Eur J Nucl Med* 1999; 26 (8): 862–868.
53. Raedler TJ, Knable MB, Lafargue T, Urbina RA, Egan MF, Pickar D, et al. *In vivo* determination of striatal dopamine D2 receptor occupancy in patients treated with olanzapine. *Psychiatry Res* 1999; 90 (2): 81–90.
54. Remington G, Kapur S, Zipursky R. The relationship between risperidone plasma levels and dopamine D2 occupancy: A positron emission tomographic study. *J Clin Psychophamacol* 1998; 18 (1): 82–83.
55. Nyberg S, Eriksson B, Oxenstierna G, Halldin C, Farde L. Suggested minimal effective dose of risperidone based on PET-Measured D2 and 5′HT2A receptor occupancy in schizophrenia patients. *ACTA Psychiatrica Scandinavica* 1999; 156 (6): 869–875.
56. Knable M, Heinz A, Raedler T, Wienberger D. Extrapyramidal side effects with risperidone and haloperidol at comparable D2 receptor occupancy levels. *Psychiatric Research* 1997; 75: 91–101.
57. Gefvert O, Lundberg T, Wieselgren I, Bergstrom M, Langstrom B, Wiesel F, et al. D2 and 5HT2a receptor occupancy of different doses of quetiapine in schizophrenia: a PET study. *European Neuropsychopharmacology* 2001; 11: 105–110.
58. Kufferle B, Tauscher J, Asenbaum S, Vesely C, Podreka I, Brucke T, et al. IBZM SPECT imaging of striatal dopamine-2 receptors in psychotic patients treated with the novel antipsychotic substance quetiapine in comparison to clozapine and haloperidol. *Psychopharmacology* 1997; 133: 323–328.
59. Kapur S, Zipursky R, Jones C, Shammi C, Remington G, Seeman P. A positron emission tomography study of quetiapine in schizophrenia. *Arch Gen Psychiatry* 2000; 57: 553–559.
60. Kapur S, Seeman P. Does fast dissociation from the dopamine D2 receptor explain the action of atypical antipsychotics?: A new hypothesis. *Am J Psychiatry* 2001; 158 (3): 360–369.
61. Davis KL, Kahn RS, Ko G, Davidson M. Dopamine in schizophrenia: a review and reconceptualization. *Am J Psychiatry* 1991; 148: 1474–1486.
62. Weinberger DR. Implications of the normal brain development for the pathogenesis of schizophrenia. *Arch Gen Psychiatry* 1987; 44: 660–669.
63. Goldman-Rakic PS, Muly EC 3rd, Williams GV. D(1) receptors in prefrontal cells and circuits. *Brain Res Brain Res Rev* 2000; 31 (2–3): 295–301.
64. De Keyser J, Ebinger G, Vauquelin G. Evidence for a widespread dopaminergic innervation of the human cerebral neocortex. *Neurosci Lett* 1989; 104: 281–285.
65. Hall H, Sedvall G, Magnusson O, Kopp J, Halldin C, Farde L. Distribution of D1- and D2-dopamine receptors, and dopamine and its metabolites in the human brain. *Neuropsychopharmacology* 1994; 11: 245–256.
66. Aghajanian GK, Marek GJ. Serotonin model of schizophrenia: emerging role of glutamate mechanisms. *Brain Res Brain Res Rev* 2000; 31 (2–3): 302–312.

67. Abi-Dargham A, Krystal J. Serotonin receptors as target of antipsychotic medications. In: Lidow MS, editor. *Neurotransmitter receptors in actions of antipsychotic medications*. Boca Raton, FL; CRC Press LLC, 2000: 79–107.
68. Lewis R, Kapur S, Jones C, DaSilva J, Brown GM, Wilson AA, et al. Serotonin 5-HT2 receptors in schizophrenia: a PET study using [^{18}F]setoperone in neuroleptic-naive patients and normal subjects. *Am J Psychiatry* 1999; 156 (1): 72–78.
69. Trichard C, Paillere-Martinot ML, Attar-Levy D, Blin J, Feline A, Martinot JL. No serotonin 5-HT2A receptor density abnormality in the cortex of schizophrenic patients studied with PET. *Schizophr Res* 1998; 31 (1): 13–17.
70. Okubo Y, Suhara T, Suzuki K, Kobayashi K, Inoue O, Terasaki O, et al. Serotonin 5-HT2 receptors in schizophrenic patients studied by positron emission tomography. *Life Sci* 2000; 66 (25): 2455–2464.
71. Ngan ET, Yatham LN, Ruth TJ, Liddle PF. Decreased serotonin 2A receptor densities in neuroleptic-naive patients with schizophrenia: A PET study using [^{18}F] setoperone. *Am J Psychiatry* 2000; 157 (6): 1016–1018.
72. Suehiro M, Scheffel U, Ravert HT, Dannals RF, Wagner H Jr. [^{11}C](+)McN5652 as a radiotracer for imaging serotonin uptake sites with PET. *Life Sci* 1993; 53 (11): 883–892.
73. Szabo Z, Scheffel U, Suehiro M, Dannals RF, Kim SE, Ravert HT, et al. Positron emission tomography of 5-HT transporter sites in the baboon brain with [^{11}C]McN5652. *J Cereb Blood Flow Metab* 1995; 15 (5): 798–805.
74. Szabo Z, Scheffel U, Mathews WB, Ravert HT, Szabo K, Kraut M, et al. Kinetic analysis of [^{11}C]McN5652: a serotonin transporter radioligand. *J Cereb Blood Flow Metab* 1999; 19 (9): 967–981.
75. Parsey RV, Kegeles LS, Hwang DR, Simpson N, Abi-Dargham A, Mawlawi O, et al. *In vivo* quantification of brain serotonin transporters in humans using [^{11}C]McN 5652. *J Nucl Med* 2000; 41 (9): 1465–1477.
76. Buck A, Gucker PM, Schonbachler RD, Arigoni M, Kneifel S, Vollenweider FX, et al. Evaluation of serotonergic transporters using PET and [^{11}C](+)McN-5652: assessment of methods. *J Cereb Blood Flow Metab* 2000; 20 (2): 253–262.
77. Oya S, Choi S, Hou C, Mu M, Kung M, Acton PD, et al. 2-((2-((dimethylamino)methyl)phenyl)thio)-5-iodophenylamine (ADAM): an improved serotonin transporter ligand. *Nucl Med Biol* 2000; 27 (3): 249–254.
78. Emond P, Vercouillie J, Innis R, Chalon S, Mavel S, Frangin Y, et al. Substituted diphenyl sulfides as selective serotonin transporter ligands: synthesis and *in vitro* evaluation. *J Med Chem* 2002; 45 (6): 1253–1258.
79. Wilson AA, Ginovart N, Schmidt M, Meyer JH, Threlkeld PG, Houle S. Novel radiotracers for imaging the serotonin transporter by positron emission tomography: synthesis, radiosynthesis, and *in vitro* and *ex vivo* evaluation of (11)C-labeled 2-(phenylthio)araalkylamines. *J Med Chem* 2000; 43 (16): 3103–3110.
80. Houle S, Ginovart N, Hussey D, Meyer J, Wilson A. Imaging the serotonin transporter with positron emission tomography: initial human studies with [^{11}C]DAPP and [^{11}C]DASB. *Eur J Nucl Med* 2000; 27 (11): 1719–1722.
81. Meltzer HY, Matsubara S, Lee JC. The ratios of serotonin2 and dopamine2 affinities differentiate atypical and typical antipsychotic drugs. *Psychopharmacol Bull* 1989; 25 (3): 390–392.
82. Meltzer HY. The role of serotonin in antipsychotic drug action. *Neuropsychopharmacology* 1999; 21 (2 Suppl): 106S–115S.
83. Trichard C, Paillere-Martinot ML, Attar-Levy D, Recassens C, Monnet F, Martinot JL. Binding of antipsychotic drugs to cortical 5-HT2A receptors: a PET study of chlorpromazine, clozapine, and amisulpride in schizophrenic patients. *Am J Psychiatry* 1998; 155 (4): 505–508.
84. Kapur S, Zipursky RB, Remington G. Clinical and theoretical implications of 5-HT2 and D2 receptor occupancy of clozapine, risperidone, and olanzapine in schizophrenia. *Am J Psychiatry* 1999; 156 (2): 286–293.
85. Kapur S, Zipursky R, Remington G, Jones C, McKay G, Houle S. PET evidence that loxapine is an equipotent blocker of 5-HT2 and D2 receptors: implications for the therapeutics of schizophrenia. *Am J Psychiatry* 1997; 154 (11): 1525–1529.
86. Singh AN, Barlas C, Singh S, Franks P, Mishra RK. A neurochemical basis for the antipsychotic activity of loxapine: interactions with dopamine D1, D2, D4 and serotonin 5-HT2 receptor subtypes. *J Psychiatry Neurosci* 1996; 21 (1): 29–35.
87. Kinon BJ, Lieberman JA. Mechanisms of action of atypical antipsychotic drugs: a critical analysis. *Psychopharmacology (Berl)* 1996; 124 (1–2): 2–34.
88. Lieberman JA, Mailman RB, Duncan G, Sikich L, Chakos M, Nichols DE, et al. Serotonergic basis of antipsychotic drug effects in schizophrenia. *Biol Psychiatry* 1998; 44 (11): 1099–1117.
89. Ichikawa J, Meltzer HY. Relationship between dopaminergic and serotonergic neuronal activity in the frontal cortex and the action of typical and atypical antipsychotic drugs. *Eur Arch Psychiatry Clin Neurosci* 1999; 249 Suppl 4: 90–98.
90. Richelson E. Receptor pharmacology of neuroleptics: relation to clinical effects. *J Clin Psychiatry* 1999; 60 Suppl 10: 5–14.
91. Dougherty D, Alpert N, Rauch S, Fischman A, editors. *In vivo neuroreceptor imaging techniques in psychiatric drug development*. Washington, DC; American Psychiatric Publishing, Inc., 2001.
92. Blier P, Pineyro G, el Mansari M, Bergeron R, de Montigny C. Role of somatodendritic 5-HT autoreceptors in modulating 5-HT neurotransmission. *Ann NY Acad Sci* 1998; 861: 204–216.
93. Martinez D, Broft A, Laruelle M. Pindolol augmentation of antidepressant treatment: recent contributions from brain imaging studies. *Biol Psychiatry* 2000; 48 (8): 844–853.
94. Artigas F, Celada P, Laruelle M, Adell A. How does pindolol improve antidepressant action? *Trends Pharmacol Sci* 2001; 22 (5): 224–228.
95. Martinez D, Hwang D, Mawlawi O, Slifstein M, Kent J, Simpson N, et al. Differential occupancy of somatodendritic and postsynaptic 5HT(1A) receptors by pindolol. A dose-occupancy study with [^{11}C]WAY 100635 and positron emission tomography in humans. *Neuropsychopharmacology* 2001; 24 (3): 209–229.
96. Andree B, Thorberg SO, Halldin C, Farde L. Pindolol binding to 5-HT1A receptors in the human brain confirmed with positron emission tomography. *Psychopharmacology*

(Berl) 1999; 144 (3): 303–305.
97. Rabiner EA, Gunn RN, Sargent PA, Koepp M, Meyer J, Bench CJ, et al. Beta-blocker binding to brain 5HT1A receptors *in vivo*—a [^{11}C]WAY 100635 PET study. *J Cereb Blood Flow Metab* 1999; 19: S324.
98. Tsukada H, Harada N, Ohba H, Nishiyama S, Kakiuchi T. Facilitation of dopaminergic neural transmission does not affect [^{11}C]SCH23390 binding to the striatal D1 dopamine receptors, but the facilitation enhances phosphodiesterase type-IV activity through D1 receptors: PET studies in the conscious monkey brain. *Synapse* 2001; 42 (4): 258–265.