

NEUROIMAGING STUDIES IN CNS DRUGS APPROVED FROM 1995 TO 2004

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ABSTRACT

BACKGROUND/AIMS: The objective of this project is to evaluate the use of the imaging modalities in development of Neuropharmacological drugs. Neuroimaging (NI) has the potential to link pharmacokinetics (PK) with pharmacodynamics (PD) and could therefore be an important aid in understanding mechanisms of action and adverse effects of drugs, as well as in identifying mechanisms for variability in drug response. Imaging can be an effective tool in optimizing Neuropharmacological drug development. **METHODS:** NDAs approved from 1995 to 2004 in the Division of Neuropharmacological Drug Products were evaluated using a survey type approach. Information collected included the stated purpose of imaging study, PK, imaging, and PD results, and whether the study was used to support dosing or the proposed indication. Evaluation included review of the NDA submission, the final label, the FDA reviews and published literature. **RESULTS:** There were 106 NDAs approved in the Neuropharmacology division. Fifteen of these NDAs included NI studies. Five of these NDAs had receptor occupancy studies and 2 were used to support the pharmacology/proof of concept. The receptor occupancy results are in reasonable agreement with the final selected doses/dose regimen. **CONCLUSIONS:** A database capturing characteristics of NI studies in drug development has been initiated. Future efforts will focus on identifying those NI characteristics in the literature and in IND/NDAs that can be used to optimize drug development.

INTRODUCTION

Development and review of the dose-response relationships and of the clinical and basic pharmacology of neuropharmacological therapies has been hindered somewhat by traditional approaches to pharmacokinetics (PK) and pharmacodynamics (PD). This is in part due to incomplete understanding of the relationship between plasma concentrations of drugs and concentrations of drugs in the brain that may differ due to differences in drug metabolism or transporters. It is also due to an incomplete understanding of the pharmacological effects of drugs or their metabolites in the brain, and how this contributes to the PD effect – either a desired therapeutic effect or an adverse effect.

Advances in imaging modalities such as positron emission tomography (PET), single photon emission computed tomography (SPECT) and magnetic resonance imaging, and the ability to label a variety of compounds for in vivo use in humans, have created a new technology for making precise physiological and pharmacological measurements. These methods provide new non-invasive ways of evaluating drug PK at the target site, information on receptor binding and degree of receptor occupancy, as well as potential biomarkers for efficacy such as information on disease modification/progression. This also provides an opportunity to finally link PK and PD for CNS-active drugs. Neuroimaging provides an exciting and potentially useful new paradigm for drug development and optimal dose selection of neuropharmacological therapies.

OBJECTIVES

- Evaluate the use of imaging modalities in development of Neuropharmacological drugs, within NDAs, INDs and literature.
- Evaluate the value of neuroimaging in NDAs, such as value for optimal dose selection.
- Establish a database for use as a reference as well as for further analysis.
- Examine the database to identify best practices to finally provide recommendations for optimal conduct and use of imaging studies to optimize neuropharmacological drug development.

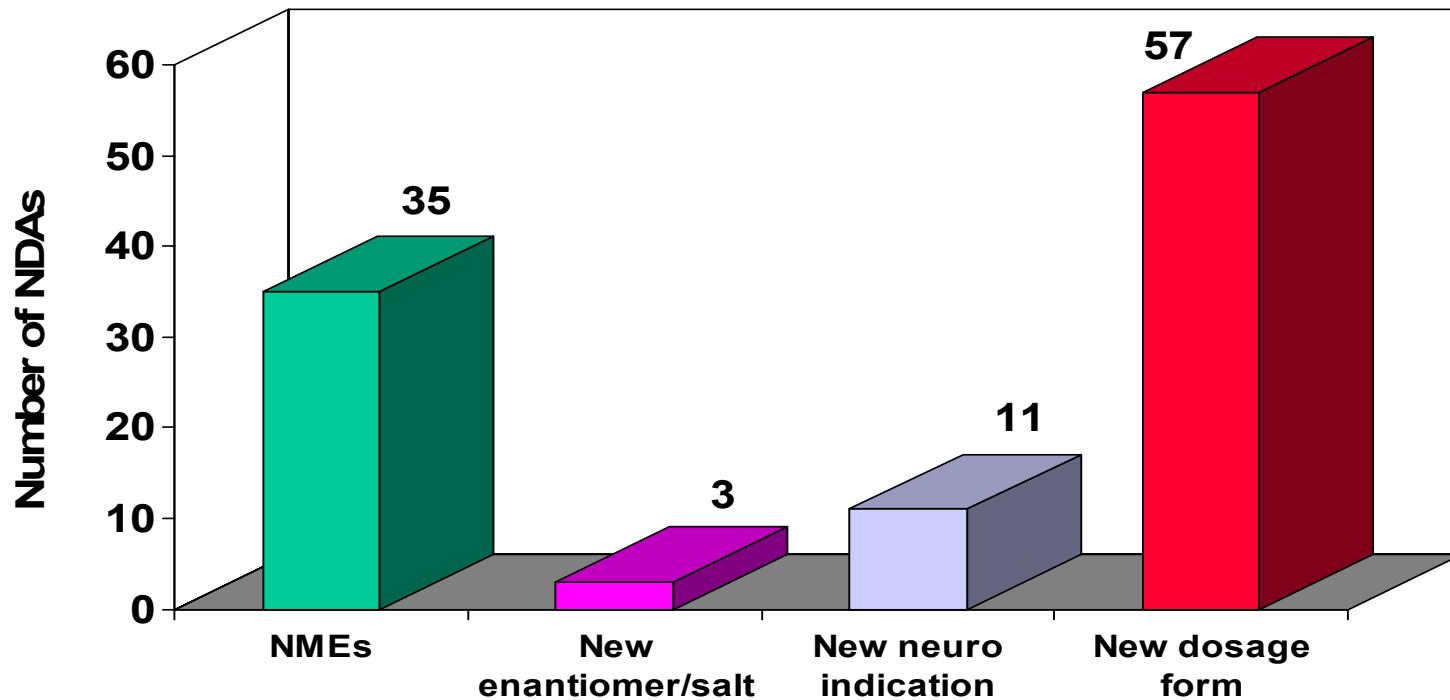
METHODS

1. The Clinical Pharmacology and Biopharmaceutics reviews of all NDAs approved from January 1995 to December 2004 in the Division of Neuropharmacological Drug Products were surveyed for imaging studies.
2. All studies containing imaging information were identified.
3. The package inserts of all these NDAs containing imaging information were examined for any pertinent labeling statements.
4. Similar information was obtained from published literature for all the identified drugs (in process).
5. A database in Microsoft Access has been set up to collect the information.
6. Information gathered in the survey includes the following:
 - Imaging and other biomarker information
 - Imaging modality
 - Purpose of the biomarker
 - PK
 - Efficacy
 - Dose-response
 - Labeling statement
 - Value of the biomarker
 - Study recommendations

DETAILED DATABASE FIELDS:

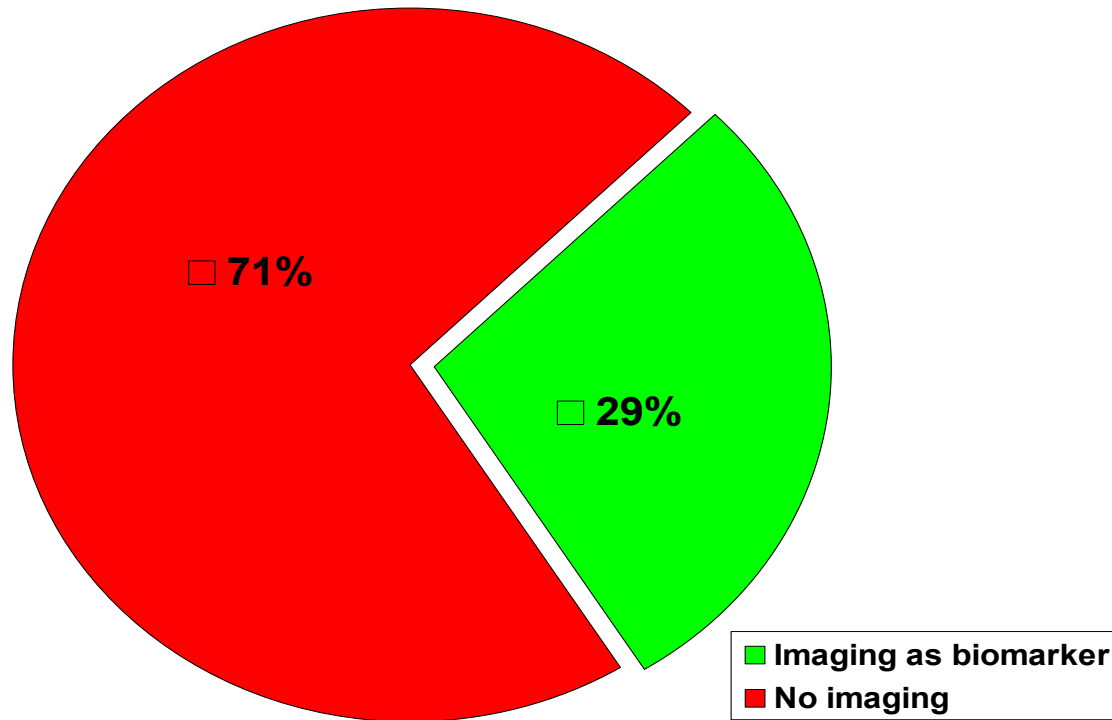
Generic name	Cmax at max approved dose
Brand name	Tmax at max approved dose
Indication	Elimination Half-Life
Drug ID	Receptor occupancy
NDA number	Route of Excretion
IND number	Unchanged %
Related NDA #	Absolute Bioavailability
Company	Relative Bioavailability
NDA submission	Food effect
NDA final decision date	Dose proportionality
Current NDA status	Metabolism - metabolites
# of prior actions	Metabolism -pathway
Basis for approval/approvable	Transporter
Approval Type	# of studies with biomarkers
Orphan drug	# of tabulated studies with imaging biomarkers
Molecular entity	# of human studies
New molecular entity	Safety#
Target	Efficacy#
Primary efficacy endpoint	
Target Class	Time to onset of action/Peak effect
Mechanism	Duration of action/peak effect
Route of administration	Duration of Trial
Imaging results support Dosage information	Value of biomarker
Biomarkers support primary clinical endpoint?	Misc comments
Dose range tested - ranging/response studies	Labeling
Dose range tested - pivotal trials	Study Recommendations

NEUROLOGY/PSYCHIATRY NDAs APPROVED 1995 TO 2004



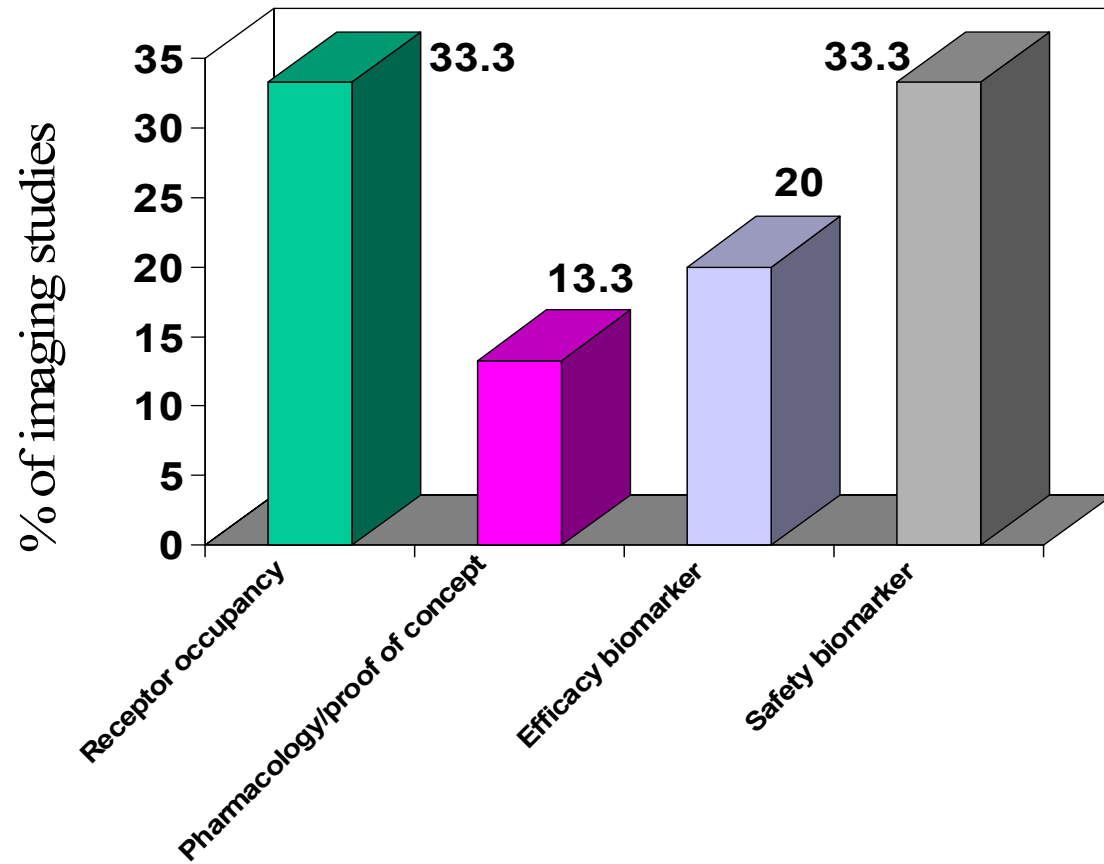
Note: some of the new indication NDAs and new dosage form NDAs contain multiple items, such as new indications and new dosage forms/strengths

IMAGING RESULTS



% of NMEs (10/35 contain Imaging information)
15 NDAs of 106 NDAs contain Imaging studies

PURPOSE OF IMAGING STUDIES



IMAGING MODALITIES

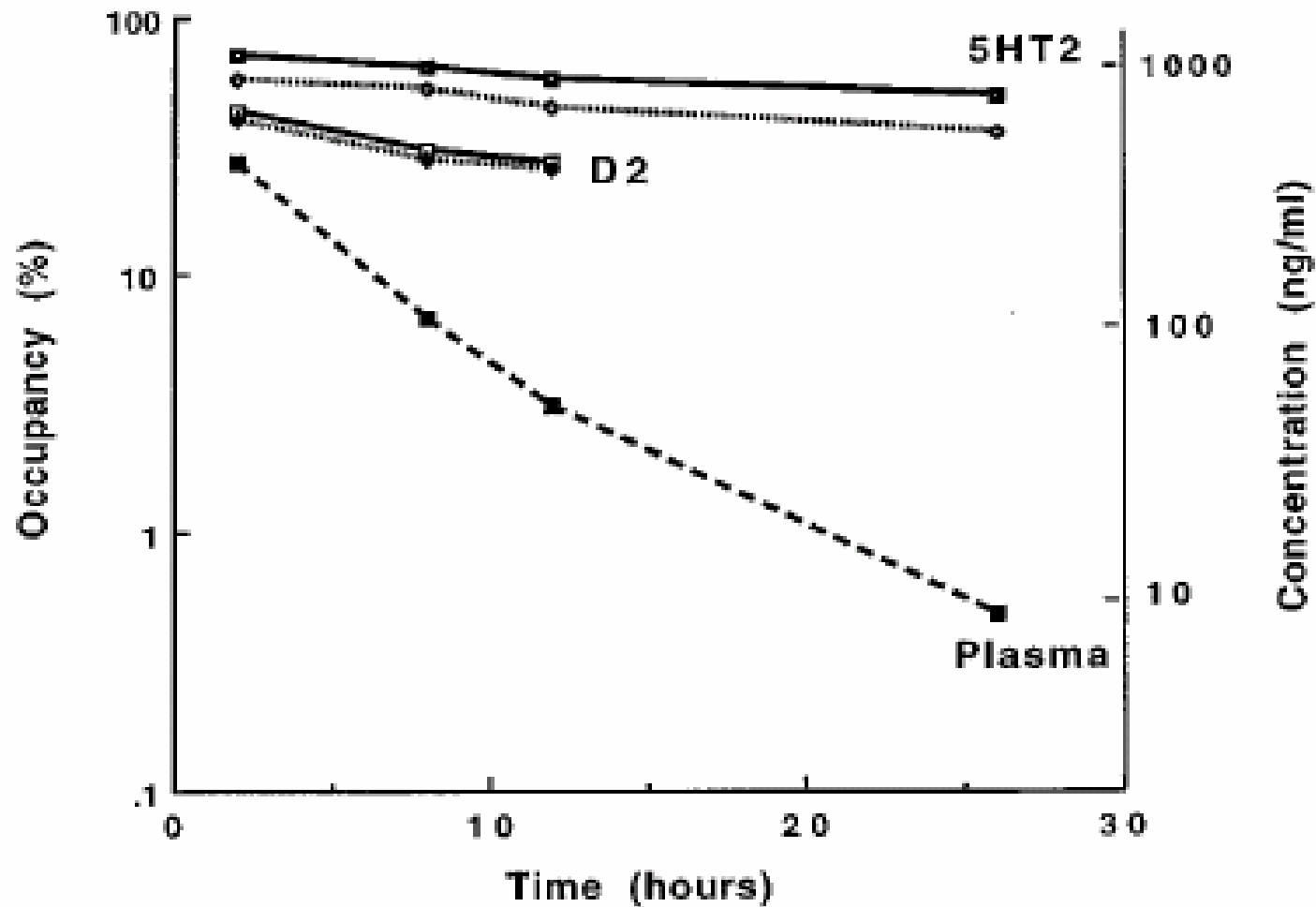
- The imaging modalities used mostly were:
 - Positron emission tomography (PET) (9 NDAs)
 - Magnetic resonance imaging (MRI) (3 NDAs)
 - Angiography (2 NDAs)
 - Ultrasound (1 NDA)
 - Spectrometry (1 NDA)
 - CT Scans (1 NDA)

IMAGING RESULTS

- Imaging studies were conducted mostly for the following therapeutic classes/indications:
 - Atypical antipsychotics (Schizophrenia)
 - Antidepressants (Major depressive disorder)
 - Multiple sclerosis
 - Triptans (Migraine)
- For the receptor occupancy studies, the receptors studied mostly were:
 - Dopamine D2
 - Serotonin 5HT2

SOME EXAMPLES OF VALUE OF IMAGING RELATED TO DOSE/REGIMEN

1. QUETIAPINE:



- Elimination half life based on plasma concentrations < 6 hours
- Using imaging as a biomarker, with D2 and 5HT2 receptor occupancy, the rate of decline in occupancy was much slower than the decline in quetiapine plasma concentrations.
- The results from imaging studies suggested that quetiapine may be clinically effective when administered on a twice daily basis.
- Approved labeled dosing regimen allows BID dosing.
- This indicates the temporal dissociation between receptor occupancy and plasma concentrations of quetiapine, supporting the value of imaging in drug development.

Figure Ref: 1. O.Gefvert et al., *Psychopharmacology* 1998; 135, pp 119-126, “Time course of Central Nervous System Dopamine-D2 and 5HT2 receptor blockade and plasma concentrations after discontinuation of quetiapine (Seroquel) in patients with Schizophrenia”.

2. Similar results were also submitted in the original NDA.

2. ARIPIPRAZOLE:

Ref: 1. F.Yokoi et al., Neuropsychopharmacology, 2002, vol. 27, #2, 248-259, Dopamine D2 and D3 Receptor Occupancy in Normal Humans Treated with the Antipsychotic Drug Aripiprazole (OPC 14597): A Study Using Positron Emission Tomography and [11C]Raclopride”

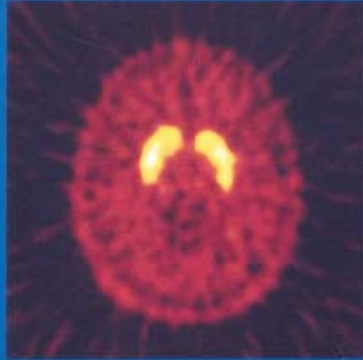
2. Similar results were also submitted in the original NDA.

Aripiprazole dose mg	Mean \pm SD D2 receptor occupancy	
	Caudate Nucleus	Putamen
0.5	39.6 \pm 5.7	39.0 \pm 4.6
1.0	47.6 \pm 4.9	53.3 \pm 6.9
2.0	78.7 \pm 3.1	71.3 \pm 6.2
10.0	86.3 \pm 3.6	83.7 \pm 10.2
30.0	84.1 \pm 11.1	93.7 \pm 1.5

- Results indicate aripiprazole enters the brain and binds to human D2 receptors in a dose-related manner that approaches saturation at the 10 mg/day dose.
- Plasma concentrations however continue to increase in a dose proportional manner in this dose range.
- Approved label indicates that the recommended starting and target dose is 10 or 15 mg/day. Doses higher than 10 or 15 mg/day were not more effective.

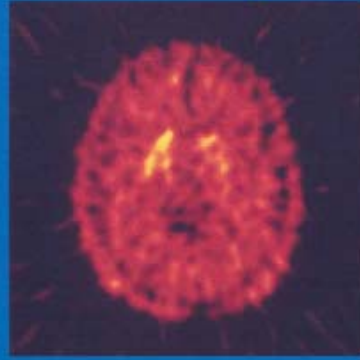
^{11}C - RAC: High Specific Activity

Pre - OPC 14,597



Baseline

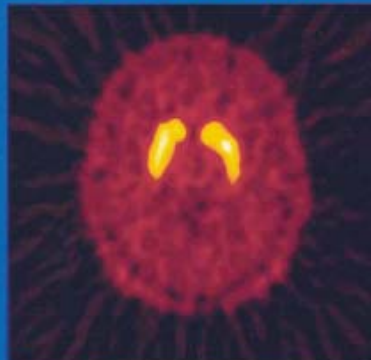
Post - OPC 14,597



2mg / day (14 Days)

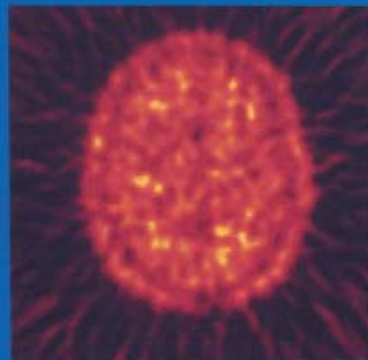
^{11}C - RAC: High Specific Activity

Pre - OPC 14,597



Baseline

Post - OPC 14,597



30mg / day (14 Days)

PET images before and after Aripiprazole

Examples in Labeling

1. In Pharmacokinetics section: *There was a dose-dependent D2 receptor occupancy indicating brain penetration of aripiprazole in humans. *Zolmitriptan nasal spray is rapidly absorbed via the nasopharynx as detected in a Photon Emission Tomography (PET) study using ^{11}C zolmitriptan.
2. In Precautions section: With zonisamide, kidney stones were detected/confirmed by sonography.
3. In Clinical trials section: For mitoxantrone, MRI based assessment of Gadolinium enhanced lesions were described.

SUMMARY & FUTURE PLANS

- A Microsoft Access based database to capture the neuroimaging studies and their characteristics in neuro drug development has been established.
- NDAs approved in the Division of Neuropharmacological Drug Products approved from 1995 to 2004 have been surveyed.
- Out of 106 NDAs approved during this period, 35 were new molecular entities. Fifteen of these NDAs had imaging used as a tool.
- Imaging was used for different purposes such as receptor occupancy, proof of concept and in some cases as efficacy and safety biomarker.
- Some examples have clearly shown that use of imaging tools provide added value in dose and dosing regimen selection which plasma concentrations alone have not been able to provide.
- Imaging methods can be used as a tool in early drug development to understand the pharmacology, mechanism of action, dose-concentration-occupancy relationship starting from preclinical studies to early human studies. This information when linked with clinical data can provide a powerful tool for optimal dosing.
- Our database along with literature search (which will be completed in the near future) can provide a powerful reference for identifying best practices and potentially validating imaging which is currently a developing exploratory biomarker.