Graphic representation of pharmacology: Development of an alternative model

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Abstract

Introduction: Providing clinicians with an easy to grasp and understandable representation of pharmacology is important to allow optimal clinical decisions to be made. Two of the most clinically relevant dimensions are receptor binding affinity and functional activity. The binding affinity for an agonist is described by the dissociation constant (K_A), and an antagonist by the inhibition constant (K_i). Functionally, medications can act as superagonists, agonists, partial agonists, antagonists, partial inverse agonists, or inverse agonists at several receptor sites, transporters, or ion channels. Comprehending the differences between agents is complicated by the number and types of binding sites.

Methods: Binding and functional data are obtained from primary literature, product labels, human cloned receptor binding, and other sources. Binding affinities are converted into ratios relative to the putative primary receptor for that category of agent. Antipsychotic binding is referenced to dopamine type 2 long (D2L) receptor binding. Binding affinity ratios (BARs) generate a 6-spoked diagram, with D2L as the hub. The most avidly bound sites are the spokes, and the disk diameter represents the BAR. Where functional data are available, they are shown as a pie chart shading the binding site's disk.

Results: Binding and function diagrams are shown for the antipsychotics where binding data are available and are compared to previous methods of pharmacologic comparisons of antipsychotics.

Discussion: Use of graphic models of psychotropic pharmacology improves clinician comprehension and may serve as an aid to improve rational therapeutics and patient outcomes.

Keywords: pharmacology, psychotropics, antipsychotics, receptor binding, functional activity, graphic comparison, dopamine, serotonin, norepinephrine, histamine, aripiprazole, asenapine, brexpiprazole, cariprazine, chlorpromazine, clozapine, fluphenazine, haloperidol, iloperidone, loxapine, lurasidone, molindone, olanzapine, paliperidone, perphenazine, pimavanserin, quetiapine, risperidone, ziprasidone, model

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Introduction

Providing clinicians with an easily grasped and understandable representation of pharmacology is a rarely achieved goal. There are many aspects of pharmacology, and providing all of the known information about a medication frequently results in obscuring and diluting the most important messages of clinical relevance. Two of the most clinically relevant dimensions are receptor binding affinity and functional activity.[1]

The binding affinity for an agonist is described by the dissociation constant (K_A) and an antagonist by the inhibition constant (K_i).[2] Functionally, psychotropics can be placed on a continuum that ranges across superagonists to agonists, partial agonists, antagonists, partial inverse agonists, and inverse agonists at each receptor site, transporter, or ion channel where there is significant binding.[3] Representing differences in just these two elements to allow a comparison between agents is
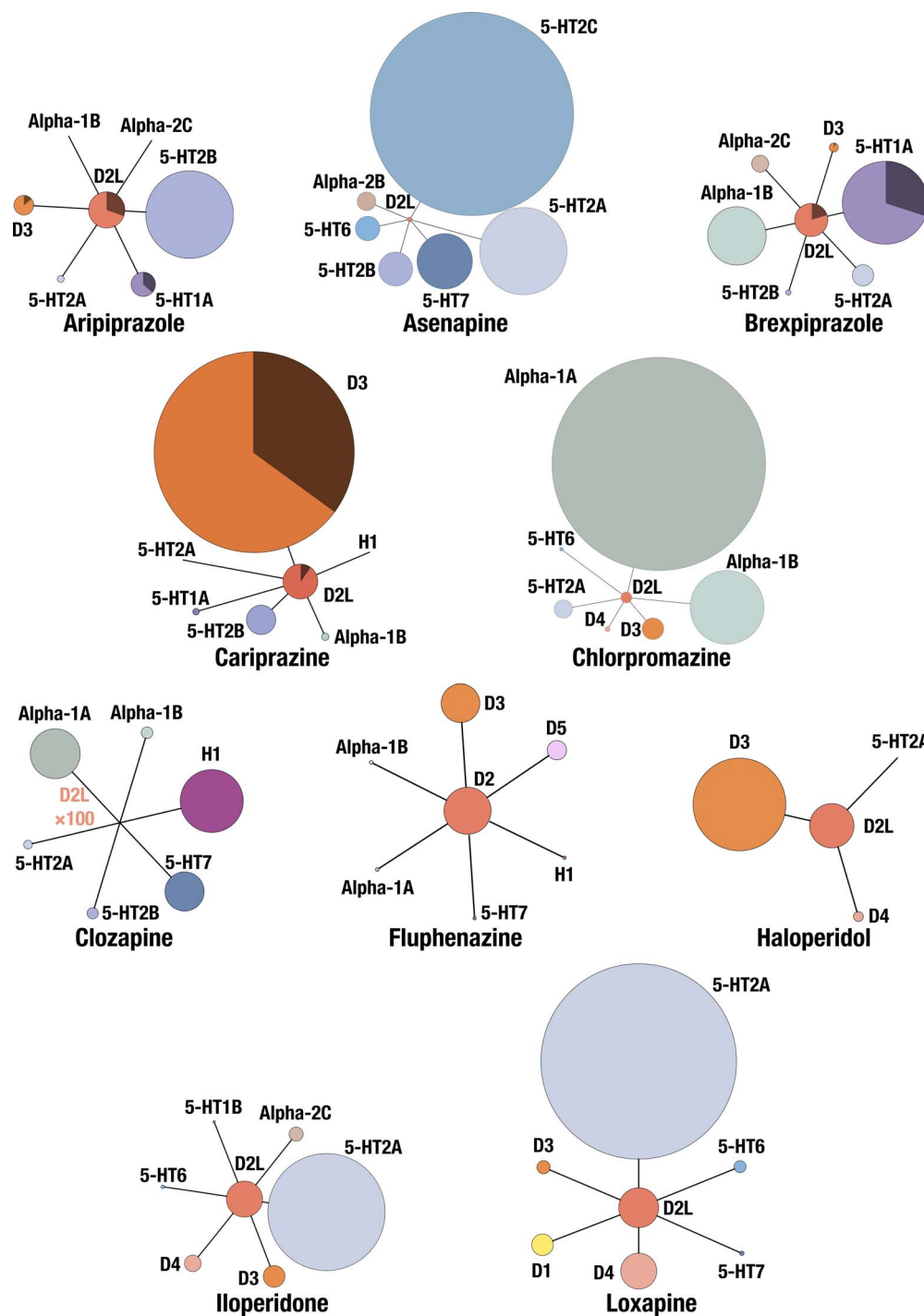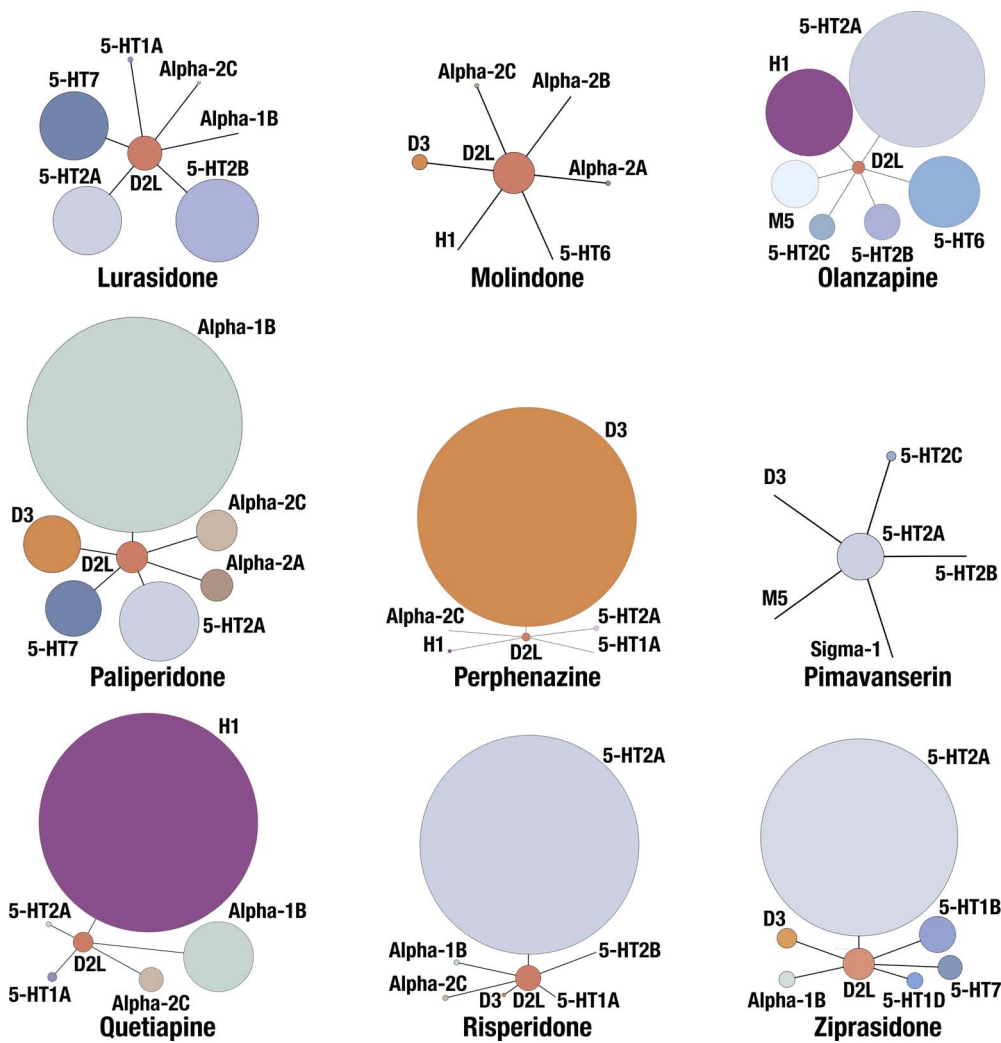
FIGURE: Graphic representation models for the antipsychotics

difficult because of the complexity created by the number and types of functional binding sites.

Developing a model to describe a drug's pharmacology is intentionally and inherently inexact. As George Box wrote, "…essentially, all models are wrong, but some are useful."[4] There have been many attempts to model psychotropic pharmacology to improve comprehension by

clinicians that have proven themselves successful by focusing on specific aspects. These include tabular data, quantitative concentration nonlinear regression plots, such as Lineweaver-Burk, or Scatchard. Others have employed proportional graphs,[5] proportional binding pie charts,[6] semiquantitative qualitative cartoons,[7] and others. Each of these excels at highlighting some aspects of the various drugs' pharmacology while having difficulty

FIGURE: Graphic representation models for the antipsychotics (continued)

incorporating other important distinctions in binding affinity or function, and in a clinically meaningful way for all medications.

This article presents an alternative graphical representation. The focus of this representation is on providing a quantitatively accurate representation of the seven most highly bound receptors in relation to the putative mechanism of action's binding site. In addition, it shows their functional pharmacology. The intent of this representation is to clearly illustrate the differences between agents in a clinically meaningful manner.

Methods

Binding data are obtained from sources such as the primary literature, product labels, human cloned receptor binding in the National Institute of Mental Health Psychoactive Drug Screening Program (PDSP).[8] When available, the PDSP-certified data are used to increase consistency between assays. When multiple studies' binding constants are available, the arithmetic mean is used. Functional data are obtained from primary literature, where available, and PDSP.[9] The binding affinity data are obtained as the K_A for agonists and as the K_i for antagonists. Both K_A and K_i are median binding values and are the most common metric used for drug-binding comparisons. Differences in the slope of the binding curve, linearity, and other details are poorly described in the literature and therefore missing from almost all model systems. The binding values are converted into binding affinity ratios (BARs) relative to the putative mechanism of action binding site for that category of agent. For the examples of antipsychotic binding shown in this article, the various compounds are referenced to dopamine type 2 long (D2L; postsynaptic) or D2 receptor binding.

Binding affinity ratios are used to generate a nominally 6-spoked diagram, with the center being D2L and the spokes the 6 most avidly bound sites. There can be fewer

than 6 spokes if there are fewer binding sites with a binding affinity ratio at least 1% of D2L.

The binding affinity is shown as a disk with the diameter determined by the BAR. Where functional data are available, they are shown as a pie chart shadow on each binding site's disk. For a full antagonist, none of the binding affinity disks is shadowed. For a full agonist, half of the disk is shadowed, and for a partial inverse agonist, more than half of the disk would be shadowed. This system permits the full range of both binding affinity and function to be displayed for the most highly bound and potentially the most clinically significant sites.

The diagrams themselves can be produced with any graphics software package that allows precise control of the diameters. The diagrams used in this article were generated with OmniGraffle (The Omni Group, Seattle, WA).

Results

Binding and function diagrams are shown for selected antipsychotics using some of the alternative models (see the Supplemental Material, available at http://dx.doi.org/10.9740/mhc.2017.09.201.s1.) and for the antipsychotics where binding data are available using this article's graphical representation (Figure) to demonstrate pharmacologic comparisons of antipsychotics. In the Figure, graphic representation models of the antipsychotics are shown in alphabetical order. Aripiprazole, brexpiprazole, and cariprazine are partial agonists at the D2L (postsynaptic) receptor, dopamine type 3 receptor (D3), and serotonin (or 5-hydroxytryptamine) type 1A receptor (5-HT1A). The functional activity is represented by shading the binding disk like a pie chart: antagonists have no shading, a full agonist would be 50% shaded, and inverse agonists would be more than 50% shaded. Therefore, it is easy to see that aripiprazole has more D2L agonist activity than brexpiprazole, which has more than cariprazine. Some drugs are not easily represented using graphic models as shown. Chlorpromazine has a very high BAR for the α adrenergic type 1A receptor (Alpha-1A). Clozapine has a BAR so small that the entire diagram had to be reduced 2 orders of magnitude in scale to be shown. This is why the D2L label is shown in the color code for the receptor instead of black like all of the other labels. Haloperidol is only bound strongly to 4 receptors, and is therefore shown with only 3 spokes. Similarly, perphenazine, pimavanserin, and quetiapine only have 5 highly bound receptors and only 4 spokes. Pimavanserin has antipsychotic properties but has significant binding only to the D3 and not the D2L receptor. Pimavanserin mechanism is believed to be primarily antagonist (shown) or

have partially inverse agonist activity at the 5-HT2A receptor, which is shown as the hub of its diagram.

Discussion

The graphical representation described provides a focus on the highest binding affinity receptors and their function. This graphical model provides a quantitatively accurate representation of the 6 most highly bound receptors referenced to the proposed mechanism of action for antipsychotics and shows the functional pharmacology to illustrate the differences between agents in a clinically meaningful manner.

The binding data used are subject to many forms of systematic and random error. These include selective use of studies, poor choice of test ligand that may not discriminate between receptor subtypes, or inclusion of clinically dubious information (using nonhuman receptors or in situ methods) permits virtually any desired relationship to be demonstrated to an unsuspecting audience. Functional data are more difficult to measure and less commonly available.

Tabular presentation of data can obscure relationships without detailed examination.[8,9] However, large amounts of highly detailed information can be included. This is useful when reporting primary data from an experiment on one or a small number of drugs or binding sites. A useful subtype of the tabular presentation is to convert the numeric data or clinical opinion into semiquantitative or rank order symbols. A common example of such symbols would be showing 1 to 4 "+," making interpretation easier with a corresponding loss of detail and, potentially, accuracy.[10]

Nontabular semiquantitative methods with a cartoon for each receptor and subtype pioneered by Stahl[7] are a very useful compromise that can provide data on many binding sites. These are the most common comparison diagrams currently in clinical use, because Stahl's books and illustrations are found to be relatively easy to read by many trainees and clinicians. Although these cartoons can show many receptors for each drug, distinctions in the relative binding constants of the receptors are poor. This poor resolution can obscure subtle relationships and differences between molecules. Shading can be used to categorize the cartoon for each binding site as a partial agonist, but again, the resolution is low.

In developing the graphic models for this article, the use of the BAR of the putative mechanisms of action to the receptor's binding affinity, instead of the absolute value of the receptor's binding, has the advantage of reducing the degrees of freedom in the information displayed and

focuses attention on the relative binding. It is important to realize this requires the assumption that the mechanism of action is *correct and the same* for all drugs of a category. If the true mechanism of action were different between agents, then the inherent assumption that the drugs would be clinically titrated to provide the same relative effect on the receptor shown as the graphic's hub would be faulty, and the contribution of the spoke receptors could be distorted.

Many important molecules, including many of the antipsychotics, have clinically significant binding to a small number of receptors that are appropriate for this graphical display model that allows clinically significant differences between antipsychotics to be readily apparent.

The number of spokes used in the diagrams represents a compromise. If more than 6 spokes were to be displayed, the model becomes too crowded for easy comprehension. Therefore, this is a fundamental limitation of this model's design. Molecules with binding to many receptors with similar or greater affinity are not modeled well. Some antipsychotics have many receptors with similar binding to D2L, and some are bound to many sites much more strongly than D2L. Consider the different representations of clozapine in the Supplemental Material and the Figure. In the Figure, the clozapine D2L BAR is more than 150 times lower than the most strongly bound receptor, histamine 1 (H1), and the graphic had to scaled 100-fold smaller than the others. In these situations, alternative representations, such as column graphs or tables, are more accurate and understandable models of binding.

The use of diameter rather than area may at first appear to be incorrect. Research has demonstrated that the longest dimension dominates the perceptual comparison between objects. When the longest dimension is used to represent the figure of merit, it provides a more accurate perception of the relationship in a graphical display.[11,12] The choice of what graphical device to use (circle, square, etc) and what dimension is most important from a perceptual basis is critical. Use of the diameters of the disks to represent the BAR allows correct interpretation. Use of a disk and the diameter is not the only option. Additional information can be incorporated into the diagram, but at the potential cost of adding confusion and creating difficulty in grasping the salient features. The 95% confidence interval of the receptor binding could be added by replacing the disk with an ellipse, with the major axis the 97.5 percentile and the minor axis the 2.5 percentile. The color is used in these diagrams to provide a distinction between the receptors represented. The specific colors used for each receptor are modeled after those used by Stahl to allow easier comparison and reduce confusion.

Obtaining reliable functional activity is currently difficult in many cases for the various binding sites. When available it can be usefully displayed by use of a superimposed pie chart shading of the BAR disk where known. Antagonists are shown without any shading, weak partial agonists (such as cariprazine at D2L) are shaded between $0°$ and $90°$, and stronger partial agonists (such as aripiprazole at D2L) are shaded between $90°$ and $180°$. A full agonist (such as dopamine) would be shown with $180°$ of shading. Similarly, inverse agonists (partial to full) would be represented with $180°$ and $360°$ of shading. Although none are shown, there is some disputed evidence that some of the antipsychotics, including pimavanserin, that are conventionally considered to be antagonists are, in fact, inverse agonists.[13,14]

Graphical representation of the pharmacology of medications is an important additional way to allow comparisons between agents. The method of generating these diagrams shows the quantitative relative binding of the most strongly bound and clinically relevant receptors and functional status. This model is widely applicable to many agents and can be used successfully by both trainees and clinicians to gain valuable insight into drug differences.

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