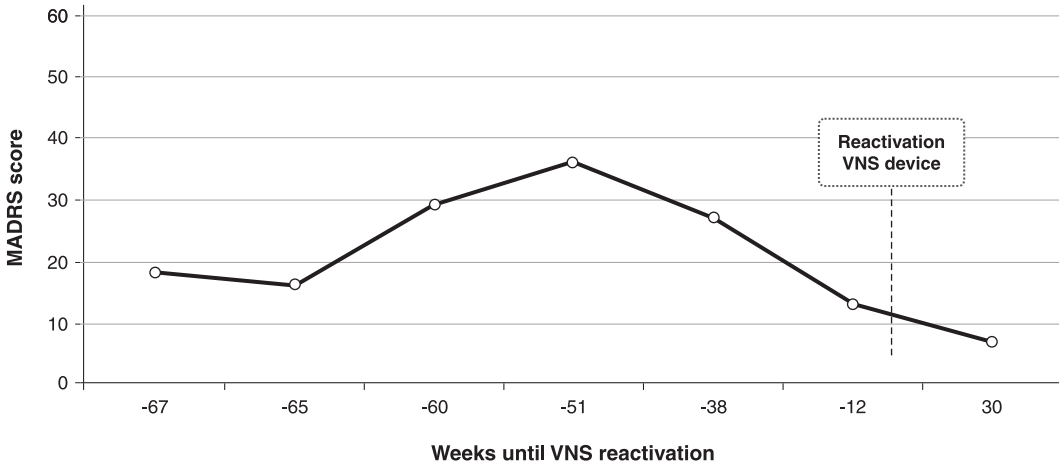

Figure 1 MADRS scores during the observation period (week 0 corresponds to VNS device reactivation).

Pharmaceuticals, and Abbvie; is a consultant for Eurofarma; is a stockholder at Instituto de Neurociencias Dr. Joao Quevedo; and receives copyrights from Artmed Editora, Artmed Panamericana, and Elsevier/Academic Press.

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Clinical perspective on antipsychotic receptor binding affinities

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The interactions between antipsychotic drugs and cell receptors can be measured as binding affinity values, expressed in terms of the dissociation constant, Kd; the inhibition constant, pKi (-log Ki); and the half-maximal inhibitory concentration, IC50. The affinity constant values (Ki) of each ligand are experimentally measured, calculated from the Cheng-Prusoff equation: Ki = IC50/(1 + C/Kd), where C is the concentration of ligand and Kd is its

dissociation constant. Each medication included in the antipsychotic class has a unique receptor-binding profile. This profile, the magnitude of the bond between ligand and targets (binding affinity or Ki), and the type of pharmacodynamic action (inverse agonism, antagonism, partial agonism, agonism) all converge to determine a specific pharmacological response. A lower Ki value indicates greater ability to bind to receptors and is associated with a more potent pharmacological action. The Ki value may be calculated from pKi:

$$pKi = -\log Ki \rightarrow -pKi = \log Ki \rightarrow 10^{-pKi} = Ki$$

Thus, higher pKi values correspond to lower Ki values, and vice versa.[1] However, we suppose that sometimes a mix-up can occur between different measures of receptor-binding affinity. For instance, in a review[2] published in 2010, Ki values for asenapine are reported as follows: D2 (8.9), 5-HT1A (8.6), 5-HT2A (10.15), 5-HT2C (10.46), α1 (8.9), H1 (9.0), M1 (5.09), while in a previous paper[3] the same numerical values described in the review mentioned above are presented as pKi, not Ki: D2 (8.9), 5-HT1A (8.6), 5-HT2A (10.2), 5-HT2C (10.5), α1 (8.9), H1 (9.0), M1 (5.09). Also, it is important to keep in mind that Ki values may be obtained under heterogeneous laboratory conditions (e.g., different tissue sources, species, and radioligands).

The purpose of our Letter is to briefly highlight the utmost importance of correctly understanding and reporting data on binding affinities and how they determine the clinical role of each antipsychotic drug. Proper knowledge of binding affinity profiles is decisive to:

i) predicting the specific efficacy of a drug on positive (e.g., antagonism and low Ki to D2), negative (e.g., high 5-HT2A/D2 ratio), and cognitive (e.g., antagonism and low Ki to 5-HT7) symptoms of schizophrenia;
ii) considering a dimensional pharmacotherapeutic approach, rather than a strictly categorical one;
iii) detecting specific propensity to trigger extrapyramidal symptoms, hyperprolactinemia, sexual dysfunctions, sedative/metabolic, and antiadrenergic/anticholinergic/antihistaminergic effects;
iv) defining the best switching strategies between different antipsychotics, choosing among abrupt switch, taper switch, cross-taper switch, or plateau-cross-taper switch;
v) predicting dopaminergic/adrenergic/cholinergic/serotonin/histamine rebound;
vi) determining the potential pharmacodynamic synergy of antipsychotic polypharmacy to choose a suitable complementary affinity profile;
vii) applying results of preclinical pharmacology studies to humans;
viii) using pharmacoepidemiologic-pharmacodynamic methods to investigate the mechanisms of adverse drug reactions recorded in pharmacovigilance databases;
ix) understanding the pharmacodynamic factors involved in pharmacogenomic-directed therapeutics; and
x) orientating clinicians toward precision medicine.[1-5]

We hope that clarifying the difference between pKi and Ki will prevent perpetuation of potential incorrectness in the scientific literature. Furthermore, some of our considerations may be applied to other drugs. We believe that having this topic clear in mind may be of crucial importance both for clinical and research purposes.

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Disclosure

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