

Review Article

Consensus nomenclature for *in vivo* imaging of reversibly binding radioligands

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An international group of experts in pharmacokinetic modeling recommends a consensus nomenclature to describe *in vivo* molecular imaging of reversibly binding radioligands.

Journal of Cerebral Blood Flow & Metabolism advance online publication, 9 May 2007; doi:10.1038/sj.jcbfm.9600493

Keywords: PET; SPECT; modeling; nomenclature; molecular imaging; radioligands

Introduction

Imaging molecular targets such as receptors with positron emission tomography (PET) and single photon emission-computed tomography strongly relies on prior decades of research using *in vitro* radioligand techniques. These *in vitro* experiments are based on the equilibrium binding reaction between receptors R and free ligand F to form the bound ligand–receptor complex B, with reaction rate constants k_{on} and k_{off} .



The term ‘binding potential’ was introduced for PET imaging and was also based on *in vitro* radioligand binding (Mintun *et al*, 1984). The concept was relatively simple and clarified the linear role of two parameters (receptor density and radioligand affinity) to determine the amount of radioligand uptake in brain. Specifically, Mintun *et al* (1984) defined binding potential as the ratio of B_{max} (receptor density) to K_D (radioligand equilibrium dissociation constant). Because affinity of ligand binding is the inverse of K_D , BP can be equivalently viewed as the product of B_{max} and affinity.

$$BP = \frac{B_{max}}{K_D} = B_{max} \times \frac{1}{K_D} = B_{max} \times \text{affinity} \quad (2)$$

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Received 29 January 2007; revised 23 February 2007; accepted 27 February 2007

The binding potential concept was embraced by the expanding field of radioligand imaging and often used as the primary outcome measure of experiments. Over several years, binding potential was defined in different ways and noted with varying abbreviations. The lack of consensus on nomenclature continues to cause significant confusion and often necessitates redundant explanations in manuscripts to clarify the specific terms used by the author. We propose a nomenclature that has broad support among experts in quantitation of *in vivo* radioligand binding.

Background

All *in vivo* studies of binding potential seek to measure a target receptor in terms of specific radioligand binding. Specific binding is defined as that associated with the target and distinct from radioligand which is free in solution or nonspecifically associated with other macromolecular components. Furthermore, the radioligand should be administered at tracer doses and thereby occupy a negligible (often defined as <5% to 10%) percentage of target sites. In this way, specific binding will reflect the entire population of target sites, without significantly perturbing the total number of available receptors. Finally, for the purpose of this presentation, we limit ourselves to radioligands that bind reversibly to a receptor, as the terms 'volume of distribution' and 'binding potential' are not useful for ligands that bind irreversibly. Note that by irreversible we mean a ligand that shows no clear evidence of dissociation over the time period of the PET or single photon emission-computed tomography study.

Cause of Discrepant Definitions

Binding potential quantifies the equilibrium concentration of specific binding as a ratio to some other reference concentration. The cause of the discrepant nomenclatures can be understood by the use of three distinct reference concentrations of the radioligand (Table 1). Because of these three reference concentrations, we recommend

three abbreviations for binding potential measured *in vivo*.

BP_F refers to the ratio at equilibrium of the concentration of specifically bound radioligand in tissue to the concentration of free radioligand in tissue, which is assumed to equal the free concentration in plasma, if the ligand passes the blood-brain barrier only by diffusion (see discussion below).

BP_P refers to the ratio at equilibrium of specifically bound radioligand to that of total parent radioligand in plasma (i.e., free plus protein bound, excluding radioactive metabolites).

BP_{ND} refers to the ratio at equilibrium of specifically bound radioligand to that of nondisplaceable radioligand in tissue. BP_{ND} is the typical measurement from reference tissue methods, as it compares the concentration of radioligand in receptor-rich to receptor-free regions.

With this nomenclature, BP without subscript refers to the 'true' *in vitro* measurement of B_{max}/K_D , and BP with subscripts refers to *in vivo* measurements that reflect, but typically do not equal, B_{max}/K_D . Specifically, these terms are proportional to the concentration of unoccupied or available receptor, B_{avail} . See below for discussion of *in vitro* versus *in vivo* measurements.

The motivation for this nomenclature is to remind the reader what factors are present in binding potential. The term BP_F reflects the ratio of specific binding to free radioligand at equilibrium. BP_P is not corrected for the fraction of ligand that is bound to plasma proteins (f_p), that is, BP_P equals the product of BP_F and f_p . BP_{ND} is not corrected for the free fraction of ligand in the nondisplaceable tissue compartment (f_{ND}), that is, BP_{ND} equals the product of BP_F and f_{ND} .

All three versions of binding potential have been used in different forms in the literature and have value depending on the particular application. For example, BP_{ND} does not require blood sampling and is relatively easy to implement. However, use of BP_{ND} as an outcome measure depends most heavily on the assumption that nondisplaceable uptake is independent of subject groups or treatment effects. BP_F and BP_P both require measurement of the arterial input function. While BP_F may be most

Table 1 Definitions of three *in vivo* binding potential values

Binding potential	<i>In vitro</i> analog	Volume of distribution	Rate constants	Specific compared to:	Units	Plasma sample?	f_p ?
BP_F	$= B_{avail}/K_D$	$= (V_T - V_{ND})/f_p$	$= \frac{K_1 k_3}{f_p k_2 k_4}$	Free plasma concentration	$\text{mL} \cdot \text{cm}^{-3}$	Yes	Yes
BP_P	$= f_p B_{avail}/K_D$	$= V_T - V_{ND}$	$= \frac{K_1 k_3}{k_2 k_4}$	Total plasma concentration	$\text{mL} \cdot \text{cm}^{-3}$	Yes	No
BP_{ND}	$= f_{ND} B_{avail}/K_D$	$= (V_T - V_{ND})/V_{ND}$	$= \frac{k_3}{k_4}$	Nondisplaceable uptake	Unitless	No	No

Rate constants are for the two-tissue compartment model. The two rightmost columns show whether each of the three binding potential values requires measurement of the concentration of radioligand in plasma (often arterial plasma) or the measurement of its plasma free fraction f_p . See Table 2 for definitions.

ideal from a theoretical view, BP_p may be more appropriate if the plasma free fraction is difficult to measure accurately or has a small range with no difference between groups, that is correcting for protein binding differences could simply add more variability to the data.

Volumes of Distribution

In clinical pharmacology, ‘volume of distribution’ typically refers to the volume of blood (or plasma) that would be required to account for the amount of drug in the entire body. For example, if the concentration of drug in plasma is $200 \text{ ng} \cdot \text{mL}^{-1}$ and 10 mg of drug are in the entire body, then its volume of distribution would be 50 L . That is, 50 L of plasma contains the same amount of drug as the entire body.

The field of *in vivo* imaging with radioligands adapted this concept in two ways. First, the target region was regarded as a particular organ (e.g., brain) rather than the entire body. Second, instead of referring to the amount of drug in the entire organ, the target was expressed as the amount of radioligand in a volume of tissue (i.e., a concentration). For example, if the concentration of a radiopharmaceutical at equilibrium is $100 \text{ kBq} \cdot \text{cm}^{-3}$ in striatum (C_T) and $5 \text{ kBq} \cdot \text{mL}^{-1}$ in plasma (C_P), then its volume of distribution (V_T) is $20 \text{ mL} \cdot \text{cm}^{-3}$. That is, 20 mL plasma would be required to account for the radioligand in just 1 cm^3 of brain. The units of this new ‘volume of distribution’ are not volume (mL) but a ratio of two volumes (mL and cm^{-3}). Furthermore, although $1 \text{ cm}^3 = 1 \text{ mL}$ by SI nomenclature (Taylor, 1995, Table 6, p. 8) and this ‘volume of distribution’ would appear to be strictly unitless, it is important to maintain the units. In summary, the volume of distribution used in most imaging studies is the ratio of the concentration of radioligand in a region of tissue to that in plasma. We express the volume of distribution in units of $\text{mL} \cdot \text{cm}^{-3}$ to clarify that it is a ratio of mL of reference fluid to a volume of tissue, where fluid volumes are measured in milliliter and physical volumes are measured in cubic centimeter from PET or single photon emission-computed tomography.

Tissue may contain radioligand that is specifically bound to receptors (S), nonspecifically bound (NS), or free in tissue water (F). Thus, the total concentration of radioligand in the tissue (C_T) can be expressed as follows:

$$C_T = C_S + C_{NS} + C_{FT} \quad (3)$$

Furthermore, nondisplaceable (ND) uptake is the sum of nonspecific (NS) and free ligand in tissue.

$$C_{ND} = C_{FT} + C_{NS} \quad (4)$$

The volume of distribution of these three components equals the ratio *at equilibrium* of each concentration to that of parent radioligand (C_P) in

plasma, separated from radiometabolites.

$$V_T = \frac{C_T}{C_P} = V_{FT} + V_{NS} + V_S = V_{ND} + V_S \quad (5)$$

$$V_{NS} = \frac{C_{NS}}{C_P} \quad (6)$$

$$V_{ND} = \frac{C_{ND}}{C_P} \quad (7)$$

$$V_S = \frac{C_S}{C_P} \quad (8)$$

Free Fractions f_p and f_{ND}

The free fraction of drug or radioligand in plasma is the fraction of the ligand that is not bound to plasma proteins at equilibrium, i.e., that which is freely diffusible in plasma water. The plasma free fraction is referred to as f_p , and the concentration of free drug in plasma C_{FP} can be calculated as

$$C_{FP} = f_p C_P \quad (9)$$

The comparable term f_{ND} is the fraction of drug that is freely dissolved in tissue water. This tissue free fraction f_{ND} is expressed relative to the nondisplaceable compartment.

$$C_{FT} = f_{ND} C_{ND} \quad (10)$$

The parameter f_{ND} is defined with respect to the nondisplaceable compartment and is, thereby, usually assumed to be equal in receptor-rich and receptor-free regions, assuming that nonspecific binding (NS) is the same in both areas.

Relation of Binding Potential to Volumes of Distribution

An important corollary of Mintun’s formulation is that binding potential equals a particular volume of distribution, namely, that of the specific (receptor bound) radioligand. The equivalence of these two concepts can be seen from the Michaelis–Menten equation describing *in vitro* receptor binding under equilibrium conditions.

$$B = \frac{B_{\max} F}{K_D + F} \quad (11)$$

where B is the concentration of receptor bound ligand, B_{\max} the density of receptors, F the concentration of free radioligand, and K_D is the dissociation constant. For low mass dose studies typical of radioligand imaging, $F \ll K_D$; thus, equation (11) reduces to

$$\frac{B}{F} = \frac{B_{\max}}{K_D} = BP \quad (12)$$

Thus, at tracer doses, Mintun’s original definition of binding potential (B_{\max}/K_D) equals the equilibrium

ratio of specifically bound ligand (B) to its free concentration (F). *In vitro* radioligand binding contains only one compartment, and no distinction is appropriate for the free concentration in plasma compared with that in tissue. Conversion of the *in vitro* terms to *in vivo* imaging is as follows:

$$B = C_S \quad (13)$$

$$F = C_{FT} \quad (14)$$

$$\frac{B}{F} = \frac{C_S}{C_{FT}} = \frac{B_{\text{avail}}}{K_D} = BP_F \quad (15)$$

Equation (15) is valid if the ligand enters and leaves tissue by passive diffusion, so that at equilibrium the free concentration in plasma equals the free concentration in tissue, that is $C_{FP} = C_{FT}$.

Note that *in vitro* assays typically use homogenized tissue in which all receptors are available to bind to radioligand. In contrast, only a subset of these receptors (B_{avail}) are available *in vivo* to bind to radioligand, since some may be compartmentalized, in a low affinity state, or occupied by endogenous transmitter.

After the pattern of clinical pharmacology, the proposed nomenclature could have used only volumes of distribution and not binding potential. Instead, we elected to use portions of both nomenclatures. Binding potential was maintained because of widespread use in imaging and its important theoretical connection to *in vitro* receptor binding (equation (11)). As binding potential refers to specific binding, additional terms are necessary to describe nondisplaceable and total uptake of radioligand into tissue. We elected to use V_T for the distribution volume of total ligand uptake in tissue relative to total concentration of ligand in plasma, since most clinical pharmacology studies use this definition. V_{ND} is the distribution volume of nondisplaceable compartment relative to total concentration of ligand in plasma, where $V_{ND} = V_F + V_{NS}$.

Because specific binding equals $V_T - V_{ND}$,

$$BP_{ND} = \frac{V_T - V_{ND}}{V_{ND}} = \frac{V_T}{V_{ND}} - 1 \quad (16)$$

The term V_T/V_{ND} is sometimes termed the 'distribution volume ratio' (DVR). BP_{ND} does not generally require arterial plasma measurements and, under typical assumptions, can be 'directly' calculated from only brain data using a variety of reference tissue methods (Gunn *et al*, 1997; Lammertsma and Hume, 1996; Logan *et al*, 1996). Nevertheless, BP_{ND} can be 'indirectly' calculated from volumes of distribution measured with arterial plasma concentrations of radioligand, as shown in equation (16).

BP refers to specific binding as a ratio to other concentrations (free in plasma, total in plasma, and nondisplaceable). In contrast V can be used for specific, nondisplaceable, or total uptake but is always a ratio to total radioligand concentration in plasma. Thus, when numerator and denominator are

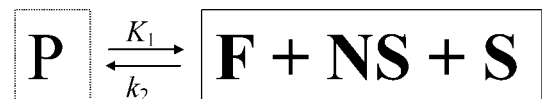
the same, this nomenclature has two redundant terms, that is $V_S = BP_P$. Nevertheless, we recommend this redundancy, because a single document may need terms for only V and another for only BP .

Units of Rate Constants

The standard one- and two-tissue compartment models used in kinetic studies are shown in Figure 1. By common practice, we recommend that the rate constant for transfer from arterial plasma to tissue (K_1) use upper case, whereas the remaining rate constants (k_2 , k_3 , and k_4) are lower case. The primary reason for this special distinction is to note that the units of K_1 are different from those of the other rate constants. K_1 commonly has units to reflect volume of blood (or plasma) per volume of tissue per minute, whereas the other transfer rate constants (k_2 , k_3 , and k_4) have units of min^{-1} . K_1 is often given in units of $\text{mL} \cdot \text{mL}^{-1} \cdot \text{min}^{-1}$, which refers to mL plasma per mL tissue per minute. However, mL is generally reserved for fluids, whereas cm^3 is used for solids (Taylor 1995, Section 8.2, p. 23). Thus, we elected units of K_1 to be $\text{mL} \cdot \text{cm}^{-3}$ to distinguish mL plasma from cm^3 tissue (Table 2).

The ratio of K_1 to the remaining rate constants will have units of $\text{mL} \cdot \text{cm}^{-3}$. As shown below, such ratios determine binding potentials and volumes of distribution, which therefore can also be considered to have units of $\text{mL} \cdot \text{cm}^{-3}$. The use of separate units for plasma (mL) and brain (cm^3) helps to clarify that the 'volumes' in volumes of distribution refer to the mL plasma required to account for ligand in 1cm^3 tissue.

A One-tissue Compartment



B Two-tissue Compartments

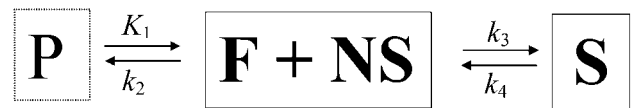


Figure 1 Common compartment models. **(A)** One-tissue compartment model. The tissue is considered to have just one compartment, that is the free and nonspecifically bound ligand cannot be kinetically distinguished from the specifically bound. This model is typically called 'two compartment' (for two 'boxes') in clinical pharmacology but 'one-tissue compartment' in radioligand imaging. **(B)** Two-tissue compartment model. Two of the compartments ('boxes') are located within the tissue: nondisplaceable, that is free plus nonspecific ($F + NS$) and specific (S). Input to the tissue derives from the plasma (P). This model is typically called 'three compartment' (for three 'boxes') in clinical pharmacology but 'two-tissue compartment' in radioligand imaging.

Relation of Compartmental Rate Constants to Binding Potential and Distribution Volume

An important concept of pharmacokinetics is that the ratio of compartmental rate constants equals selected equilibrium distribution volumes. The derivation of these relationships is included in many publications (see, e.g., Koeppe *et al*, 1991; Lassen, 1992). Using the current nomenclature, the resulting equations for *BP* are included in Table 1 in terms of volumes of distribution. For one- and two-tissue compartment models, volumes of distribution can be calculated from rate constants as follows.

One-tissue compartment model:

$$V_T = \frac{K_1}{k_2} \quad (17)$$

Two-tissue compartment model:

$$V_T = \frac{K_1}{k_2} \left(1 + \frac{k_3}{k_4}\right) \quad (18)$$

$$V_{ND} = \frac{K_1}{k_2} = \frac{f_P}{f_{ND}} \quad (19)$$

Equation (19) can be derived from equations (9) and (10) under the assumption that at equilibrium, if the ligand enters and leaves tissue by passive diffusion, the free concentration in plasma equals the free concentration in tissue, that is $C_{FP} = C_{FT}$. Note that strictly this is not the case, but rather the concentration at equilibrium in the aqueous phase of plasma is equal to the concentration in the aqueous phase of tissue. As the aqueous volume fractions in plasma and tissue differ, we should add these volume fraction terms to equation (19). However, we chose to leave equation (19) in this form, with the proviso that, strictly, f_P and f_{ND} are not dimensionless, but include the correction for aqueous volume fractions in plasma and tissue. Note that both these fractions are close to 1.0.

Relation of *In Vitro* Receptor Binding to Kinetic Parameters

The central concept of the *in vivo* binding potential is that it measures the ratio of the available receptor density to the equilibrium dissociation rate constant, both of which had been investigated in prior decades using *in vitro* techniques. Most investigators think that radioligand measurements of binding potential reflect B_{avail}/K_D , although the subtleties of the *in vivo* condition continue to be investigated actively. The *in vivo* rate constants have also been compared with *in vitro* rate binding constants. With the assumptions that the *in vivo* k_4 equals the *in vitro* k_{off} and that the free and nondisplaceable ligand are in rapid equilibrium,

the relevant equations for the two-tissue compartment model are shown below.

$$\text{In vitro} \quad K_D = \frac{k_{off}}{k_{on}} \quad (20)$$

$$\text{In vivo} \quad k_3 = f_{ND} k_{on} B_{avail} \quad (21)$$

$$k_4 = k_{off} \quad (22)$$

If these *in vivo* equations for k_3 and k_4 are substituted in Table 1 (column of rate constants), they do mathematically confirm that $BP_F = B_{avail}/K_D$, under the assumption of passive diffusion of the radioligand across the blood–brain barrier. Nevertheless, several radioligand studies suggest that the *in vivo* k_4 is much smaller than the *in vitro* k_{off} , as stated in equation (22). That is, the *in vivo* rate of dissociation (k_4) is much slower than the *in vitro* rate (k_{off}). This phenomenon has been shown for several neuroreceptor ligands in which displacement of the radioligand occurs far more rapidly than could be attributed to the slow k_4 rate measured in typical baseline conditions of negligible receptor occupancy (Laruelle *et al*, 1994; Robertson *et al*, 1991). Despite this apparent discrepancy between k_4 and k_{off} , both k_3 (which posited as a function of three variables) and k_4 appear to be similarly decreased by a constant factor such that their ratio is proportional to the *in vivo* K_D , which sometimes approximates that found *in vitro*. The cause of this apparent proportional scaling in k_3 and k_4 is unknown but has been ascribed to radioligand rebinding in a relatively isolated compartment referred to as the synaptic barrier (Delforge *et al*, 1996; Votaw *et al*, 1993).

The total available receptor concentration (B_{avail}) can be measured *in vivo* if imaging is performed at multiple specific activities, that is by varying the occupancy of the receptor by the radioligand. Such studies may be useful to help elucidate the differences between *in vitro* and *in vivo* conditions.

In summary, most researchers think that BP_F reflects *in vivo* measurements of B_{avail} and K_D . Nevertheless, conditions for *in vivo* radioligand binding may differ in many ways from the controlled *in vitro* environment, including temperature, multiple compartments, receptor trafficking, phosphorylation state, and competition with endogenous neurotransmitter. Although the result of complex conditions, *in vivo* radioligand binding can sometimes monitor important parameters like competition with the endogenous transmitter (Laruelle, 2000).

Receptor Occupancy and Displacement

A wide variety of imaging studies are aimed at measuring changes in occupancy of receptors owing to exogenous drugs or endogenous neurotransmitters.

Table 2 Abbreviations and units*Variables: italic font*

Abbreviation	Description	Units or not applicable
B_{\max}	Density of receptors <i>in vitro</i>	Often pmol per mg protein
B_{avail}	Density of receptors available to bind radioligand <i>in vivo</i>	molar (often $\text{nmol} \cdot \text{L}^{-1}$, i.e., nmol receptor per $1,000 \text{ cm}^{-3}$ tissue)
BP	<i>In vitro</i> binding potential	unitless
BP_{F} , BP_{P} , and BP_{ND}	<i>In vivo</i> binding potentials (see Table 1)	unitless or $\text{mL} \cdot \text{cm}^{-3}$
C	Concentration—as in C_{P} , C_{ND} , C_{S} , C_{FT} , and C_{NS}	$\text{Bq} \cdot \text{mL}^{-1}$ or molar
ΔBP_{F} , ΔBP_{P} , and ΔBP_{ND}	Percent change in binding potential caused by occupancy or displacement	%
f_{P}	Free fraction in plasma	unitless ^a
f_{ND}	Free fraction in nondisplaceable compartment	unitless ^a
K_1	Rate constant for transfer from arterial plasma to tissue	$\text{mL} \cdot \text{cm}^{-3} \cdot \text{min}^{-1}$
k_2 , k_3 , k_4	Rate constants	min^{-1}
$K_{\text{D}} = k_{\text{off}}/k_{\text{on}}$	Dissociation constant	molar (often $\text{nmol} \cdot \text{L}^{-1}$)
k_{off}	<i>In vitro</i> dissociation rate constant	min^{-1}
k_{on}	<i>In vitro</i> association rate constant	$\text{nmol} \cdot \text{L}^{-1} \cdot \text{min}^{-1}$
V_{T} , V_{S} , V_{ND} , and V_{NS}	Volumes of distribution expressed relative to total plasma ligand concentration C_{P}	$\text{mL} \cdot \text{cm}^{-3}$

Subscripts: normal font

Abbreviation	Description
FP	'Free' radioligand in plasma, as in C_{FP}
FT	'Free' radioligand in tissue, as in C_{FT}
ND	Nondisplaceable tissue uptake, as in V_{ND} and C_{ND}
NS	Nonspecific ligand binding, as in V_{NS} and C_{NS}
P	Plasma free plus protein bound, as in C_{P}
S	Specific (i.e., receptor) bound ligand, as in V_{S} and C_{S}
T	Total radioligand in tissue (i.e., free plus bound), as in V_{T} and C_{T}

^aFree fractions include correction for aqueous fraction in plasma and tissue (see text for details).

For example, in clinical pharmacology, the effects of drugs are related to the percentage of receptor sites occupied by the drug. This receptor occupancy can be defined as

$$\left(1 - \frac{B_{\text{avail}}(\text{treatment})}{B_{\text{avail}}(\text{baseline})}\right) \times 100\% \quad (23)$$

where $B_{\text{avail}}(\text{treatment})$ is the density of available receptors under the drug treatment condition. The *in vivo* experiment can be used to measure a percentage change in binding potential owing to reduced receptor availability and can be measured with BP_{F} , BP_{P} , or BP_{ND} :

$$\Delta BP_{\text{X}} = \left(1 - \frac{BP_{\text{X}}(\text{treatment})}{BP_{\text{X}}(\text{baseline})}\right) \times 100\% \quad (24)$$

where BP_{X} denotes one of the binding potential formulations. The percent change in BP_{X} and receptor occupancy will be equivalent under ideal conditions if the other parameters contributing to BP_{X} (e.g., K_{D} or f_{P}) do not change between control and treatment conditions. In addition, if ΔBP_{X} is not asymptotic to 100% at progressively higher drug concentrations, then some correction is necessary to estimate receptor occupancy from ΔBP_{X} .

Summary

The field of *in vivo* radioligand imaging has generated several different nomenclatures and abbreviations (see Table 2). We did not review these variations, so as not to confuse the reader. We think that these varying nomenclatures are confusing and detrimental to the field. Thus, we recommend the consensus nomenclature in this manuscript to improve the clarity of communications. We provide terminology for only two compartmental models (i.e., one- and two-tissue) and recognize that additional models and new discoveries will require additional terms. We hope that this basic structure will provide a useful pattern for future additions to this nomenclature.

Disclaimer

Although this article was written as part of Dr Innis's official duties as a government employee, the views expressed in this article do not necessarily represent those of NIMH, NIH, HHS, or the United States Government.

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