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Pharmacokinetics and Pharmacodynamics of Drugs in the Central Nervous System in Clinical Practice

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ABSTRACT
Despite contributing extensively to the global ailment burden, translating innovative therapeutic strategies for central nervous system (CNS) diseases from animals to people remains complicated, with a high attrition rate in the development of CNS drugs. Clinical trial failures for CNS treatments can be partially explained by factors linked to pharmacokinetics/pharmacodynamics (PK/PD), such as lack of efficacy or incorrect baseline dosage selection. In first-in-human research of CNS-acting drugs, a targeted assessment is required to identify changes in PK/PD from animal models and to select the optimum dose. In this review, we outline the available data from human trials on the PK and PD of medications in brain tissue, cerebrospinal fluid, and interstitial fluid used in the treatment of psychosis, Alzheimer's disease, and neuro-HIV, and address main aspects in the field. We also investigate at newer ways for evaluating PK/PD relationships, which may lead to optimal dose selection in CNS drug development.

I. INTRODUCTION

Brain disorders contribute to an oversized proportion of the worldwide illness burden. over one billion people worldwide suffer from psychiatric, neurological, developmental, and drug dependency disorders (1). These were the top causes of years lived with disability (YLD) worldwide in 2010, accounting for nearly 30 minutes of all YLDs (2). However, developing drugs for the CNS could be a vast challenge. These projects have a lower clinical approval rate (6 vs. 13%) and a extended time to market (12 vs. 6–7 years) than non-CNS drug development (3-6). As a result, several drug development programmes within the neurosciences (7-9) are fired, reflective a dishonest future for novel analysis in CNS disorders.

The high rate of CNS therapies is attributed to problems in deciding initial drug dose, undesirable toxicities, and an absence of efficacy (10). A correct concentration–effect analysis will offer valuable, predictable information regarding the therapeutic and adverse effect profile of a drug over a wide dose range which will greatly benefit the event of CNS-acting drugs. However, consistent with a 2007 report, human investigations yielded only a few sets of pharmacodynamic (PD) information over a wide range of dosages or concentrations (11). Though animal models square measure used to evaluate concentration–effect relationships however do not perpetually always presume human illness, particularly in the case of CNS disorders (12). Drug exposure in the human brain varies from that in animals (13) due to variations in BBB permeability, drug metabolising enzymes and transporters, and only rarely can drug be sampled from the human brain for pharmacokinetic (PK) measurements. Moreover, animal models might solely fit some mechanisms of human CNS illness or contain targets not seen in humans, complicating the interpretation of novel treatment efficacy and/or toxicity. As a result, a targeted (PK/PD assessment in humans is needed to spot variations from animal models and adjust dose to resolve these considerations. To improve the understanding of pharmacology within the CNS, researchers have used alternative approaches such as in vitro systems, translational studies, and in silico modelling.

This review is split into three sections. In Sect. 3, the present methods to measure PK and PD in brain tissue, cerebrospinal fluid (CSF), and interstitial fluid (ISF) are discussed. Whereas there is a lot of PK/PD information from animal models within the CNS, incomplete data is available from human studies. In Sects. 4–6, we have a tendency to investigate at clinical PK/PD analyses for antipsychotics, anti-medicines, Alzheimers and antiretrovirals (ARVs) at key target sites in the

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CNS, and valuate the worth of existing data and the need for future research to answer crucial queries in the area. Available animal data are presented and cautiously evaluated for clinical relevance in the absence of clinical evidence. Finally, in Sect. 7, innovative strategies for improving CNS drug development are reviewed.

Methodology

An extensive literature search was conducted to discover research articles and conference abstracts published in EMBASE (containing items in the MEDLINE database) using terms for medications used to treat disorders of the brain and CNS, paired with phrases for PK or PD, and terms for the brain and CNS. The electronic supplemental material has a complete search method. These investigations were enhanced by targeted searches in the PubMed and Google Scholar and Google Books databases, which included terms from the entire search strategy as well as additional terms for Metrics of PK or PD, or parameters affecting these measures. Additional relevant papers were found by hand searching the bibliographies of pertinent review articles.

Considerations in Pharmacokinetics (PK) and Pharmacodynamics (PD) for Drugs Acting on the Central Nervous System (CNS)

■ **Studies of Drug PK in the CNS**

Several approaches have been used to assess drug distribution into the CNS, such as evaluating drug uptake in cultured brain cells (in vitro), measuring drug concentration in brain tissue (ex vivo) and measuring drug concentration in CSF or ISF (in vivo).

For determining the extent to which investigational medications cross into the brain, in vitro BBB models are utilised as a first-line technique (14). There are several validated BBB models from several species (15), and while no ideal cell line exists, the human immortalised endothelial cell line hCMEC/D3 is the most extensively utilised and well-characterized. hCMEC/D3 experiments can be used to assess drug permeability, detect relevant drug efflux transporter interactions, quickly screen drug candidates for CNS activity, and conduct preliminary PK studies; nevertheless, these models are a static measure of drug PK. These models, in particular for anti-infectives, do not account for time-dependent death and thus may be less clinically relevant. In vitro systems also don't fully imitate all in vivo characteristics of the BBB. For example, hCMEC/D3 is more 'leaky' than the BBB and can express fewer levels of BBB-specific enzymes and drug transporters (15). As a result, in vitro systems may need to be modified, such as co-culture with other brain cells, to replicate BBB tight junctions (16). BBB-on-a-chip and neurovascular unit-on-a-chip (17) are two new microfluidic technologies that offer to simulate the dynamic in vivo environment.

Ex vivo strategies for assessing drug concentrations in brain tissue include surgical resection and postmortem. Liquid chromatography–mass spectrometry (LC–MS) examination of brain tissue homogenates provides the bulk of PK information. interstitial fluid (ISF) and intracellular fluid (ICF) concentrations square measure calculated based on these measures (18). Despite their widespread use, these methods do not generate data on drug location. MS imaging has emerged as a tool for quantifying drug molecules and spatially visualising drug distribution in tissue slices using mass spectrometry (19). MS imaging has the advantage of being able to capture drug distribution patterns in different components of a tissue (20). As an example, the antitubercular drug pretomanid was known to be primarily localised within the corpus callosum of Sprague–Dawley rats using matrix-assisted laser desorption ionisation (MALDI) MS imaging (21). According to serial sections obtained at different time points, it was observed pretomanid distributed into the corpus callosum 1–2 h after an intraperitoneal dose of 20 mg/kg, then subtle into different areas of the brain at later time points. With advancements in imaging technology, this technique could also be used to image intracellular drug concentrations and may be combined with PD targets by immunohistochemistry (IHC) or in situ hybridization in contiguous slices. Whereas this has not however been demonstrated for brain cells, Aikawa et al. utilized hematoxylin and eosin (H&E) staining, also as immunohistochemistry (IHC) staining, for CD31 and multidrug resistance transporter 1(MDR1) to reveal the co-localization of the malignant tumor drug alectinib with blood arteries in murine brains (22). Ex vivo imaging has the disadvantage of being a static measurement, requiring a composite of numerous images from different animals to get data during a dosing interval. Longitudinal data on drug disposition is determined utilizing in vivo imaging techniques like positron emission tomography (PET). PET may be a non-invasive imaging technique that

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permits the detection of radiolabeled ligands over time. It has been used to estimate PK parameters and target occupancy of varied CNS-acting medicines also as quantify absolute spatial concentrations of medicines. Whereas a comprehensive discussion of PET is on the far side the scope of this study, the reader is directed to a 2013 review (23) for a whole summary of decisive PK parameters using PET investigations. PET scans are overpriced, restricted to fewer patients because of the employment of radioactivity, and may not distinguish between parent molecule and metabolites, despite the spatial benefits and pertinence to human investigations.

Drug penetration into CNS fluid compartments is measured by several in vivo drug estimation methods. Microdialysis is a method of measuring the protein-unbound concentration in the ISF by introducing a dialysis probe into the cerebral area of the brain. This approach is commonly used in animal models for continuous drug concentration monitoring, however it is only applicable in humans during surgical procedures (24). Furthermore, because of non-specific binding to the microdialysis probe and poor drug recovery from the fluid, this approach may not be appropriate for monitoring the concentration of highly lipophilic or protein-bound drugs (24,25). Moreover, this technique does not capture intracellular active metabolites.

Drug sampling in the CSF is the most commonly known method for obtaining PK data. For a single sample, lumbar puncture is used, while spinal catheterization in the subarachnoidal space is used for continuous sampling. Lumbar punctures are less invasive than microdialysis, but they are traumatic and include medical complications, therefore they are not carried out on regularly basis. Furthermore, lumbar puncture concentrations can vary depending on the location and time of measurement (13). For example, phenytoin was predicted to reach a 300 % higher concentration in cranial CSF than spinal CSF (26) using a mathematical model. Unbound CSF concentrations are commonly employed as surrogates for unbound brain tissue concentrations in animal models (27) based on the 'free drug hypothesis,' which states that protein-unbound drugs flow from the plasma through the BBB and blood–CSF barrier (BCSFB) into the brain and CSF (28). However, there are two notable exceptions to this generalisation for some drugs (29,30): (i) drugs that utilise membrane transporters for influx and efflux (e.g. antidepressants, antiretrovirals); and (ii) drugs with poor permeability to penetrate the BBB when CSF bulk flow surpasses passive diffusion of the component into CSF (31). CSF concentrations tend to overestimate ISF concentrations (32) for efflux membrane transporter substrates such as P-glycoprotein (P-gp). While the actual rationale for this observation is uncertain, some possibilities include P-gp subapical or apical localisation on the choroid plexus resulting in drug transport and accumulation into the CSF (33), or P-gp nonfunctionality at the BCSFB (34). Because CSF is recycled at a quicker rate than ISF, it serves as a 'sink' for drug clearance (31). This effect is minimal for high permeability substances, but CSF concentrations underestimate brain or ISF concentrations for low permeability chemicals (e.g. morphine-6-glucuronide). As a result, unbound concentration in the brain may differ from the CSF concentration and perplex target site assumptions.

In case of in vivo measurements obtained at a single time point, the drug concentration in the brain or CSF can be standardised to a plasma concentration collected at the same time. While this is a standard method of determining the extent of drug uptake into the CNS and allowing for drug comparisons, the rates of drug entry and drug clearance in plasma, CSF, and brain compartments differ (35). For example, for ciprofloxacin, the CSF:plasma concentration ratio increases by as much as 1400 % in about 24 hours (35). One way to avoid this perplexing is to define the drug's full PK profile in the CSF and plasma using sparse serial sampling in a group of animals or humans, and then compute the ratio of drug exposure in the two compartments by measuring the area under the concentration–time curve. This strategy has been used for numerous anti-infective drugs when CNS infections need to be monitored (37) or excess CSF fluid needs to be drained (38,39) during ventricular catheterization. Because it's difficult to get many CSF samples from patients, population PK modelling has been applied with sparse CSF and plasma collection to get exposure profiles for medications like abacavir (40).

■ Drug Concentrations: Intracellular vs Extracellular

It's important to differentiate between extracellular and intracellular CNS drug concentrations once examining the location of action. It is most well-liked to assess drug concentration inside the ISF where the PD impact is exerted for medication that act on receptors on neuronal cell membranes like antiepileptic drugs

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(AEDs) and anti-Alzheimer's medication. Extracellular-acting medication are tested in homogenates of brain tissue, however this approach could also be deceptive. ISF concentrations are overestimated by brain tissue homogenate for AEDs and alternative basic medication (pKa > 7) where brain volume of distribution is larger than brain water volume (0.8 mL/g) because of non-specific binding in brain tissue (41,42). For anti-infective and tumor medication that act on intracellular targets, the unbound intracellular drug concentration is that the foremost relevant PK measure related to activity. Friden and colleagues incontestible a technique for estimating the concentration of unbound intracellular medication indirectly. during a nutshell, the amount of unbound drug distribution within the brain ($V_{u,brain}$) is measured in vitro in brain slices from drug-naive animals incubated in drug-containing buffer (brain slice method) (43), and conjointly the fraction of unbound drug within the brain ($f_{u,brain}$) is measured by adding drug to brain homogenates from drug-naive animals (18). Eq. 1 shows the relation of intracellular to extracellular unbound drug concentration ($K_{p,uu,cell}$).

$$K_{p,uu,cell} = V_{u,brain} \times f_{u,brain} \quad [1]$$

Gabapentin, oxycodone, morphine, and pain pill intracellular drug concentrations were ascertained to be relatively high than extracellular drug concentrations utilizing this approach (18).

■ Factors Influencing Drug PK in the CNS

Drug exposure in the CNS is influenced by a variety of factors. The reader is directed to two outstanding evaluations for a more in-depth review at individual drug classes (36,44).

A. Protein binding : Drug entry and action in the CNS are influenced by protein binding. Drugs that are intensely protein bound in the plasma concentrate, to a lesser extent, in the CSF and brain tissue. In contrast, plasma protein binding is lower for drugs that accumulate intracellularly in brain tissue, such as gabapentin and morphine (3% for gabapentin and 20% for morphine). The degree of protein binding varies depending on the concentration of drug-binding proteins in plasma, CSF, and tissue. Albumin concentrations in plasma range from 35 to 50 g/L, while CSF values are <250 mg/L. The concentrations of alpha 1-acid glycoprotein (AAG) in plasma and CSF are around 0.77 g/L and 8.4 mg/L, respectively (31). Microglial cells can produce these proteins as well (45). As a result, whereas highly protein-bound drugs(>95% protein binding) like efavirenz and fluoxetine have lower total drug concentrations in the CSF compared to the plasma, protein-unbound drug concentrations are comparable in both fluids. In general, using unbound drug concentrations in the CSF results in mechanistic PK/PD correlations (46) and improved cross-species (47) translatability.

B. Drug Efflux Transporters : MDR1 (P-gp), BCRP, and multidrug resistance protein 4 (MRP4) are all highly expressed drug efflux transporters at the BBB (48-50). On the surface of astrocytes (48), MDR1 and MRPs have also been speculated. MDR1 KO raises brain concentrations of MDR1 substrates by 10- to 100-fold (51), according to studies utilising transporter knockout (KO) mice, whereas KO of BCRP and MRP4 has minimim effect (52,53). As a result, MDR1 inhibition could be a viable strategy for enhancing the CNS exposure of drugs in rodent models. It has been shown that coadministration of MDR1 inhibitors (e.g. cyclosporin or zosuquidar) enhances penetration of MDR1 substrates such as nelfinavir or paclitaxel (54) in CNS. When the MDR1 inhibitor ritonavir was given concurrently with indinavir (55), it accelerated CSF penetration in HIV-infected patients. Although plasma exposure increased, the rise was due to a fivefold increase in trough concentration. Linear regression analysis revealed that the rise in CSF concentrations (2.67-fold) could not be explained solely by the increase in plasma concentrations, and inhibition of efflux transporters at the BBB could possibly contribute to increased indinavir CSF exposure.

C. Physicochemical properties : Drugs that are lipophilic have a higher permeability via the lipophilic BBB. The log brain uptake index (BUI) of estradiol in Sprague–Dawley rats was 232 times higher than sucrose (56) in a study of substances ranging from very polar (sucrose, logD = -4.49) to highly lipophilic (estradiol, logD = 4.14); although a greater lipophilicity also leads to a higher degree of non-specific tissue binding (57). In the analysis of seven compounds that varied in BBB permeability by

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160-fold, the highly lipophilic compound fluoxetine exhibited the greatest permeability through the BBB (evidenced by the highest permeability surface area product of 600 mL/kg*h) of Sprague–Dawley rats but a free drug fraction (0.23%) (58) that was lower than plasma (6–15%). Similarly, efavirenz penetrates through the BBB with a permeability surface area product of 2.4 mL/kg*h and a free fraction of only 0.197 % (59) in rat brain tissue, relative to 1% in blood plasma.

■ Studies of Drug PD in the CNS

In CNS disorders, number of PD targets are used. The common clinical PD endpoints are summarised in the following section. Table 1 summarises the benefits and drawbacks of these measures.

A. Receptor Occupancy/Binding Affinity :In vitro, receptor binding affinity is a measure of the concentration of ligand that results in a ligand–receptor complex, whereas receptor occupancy is the fraction of receptors that have formed a ligand–receptor complex in vivo compared to baseline receptor density. The binding affinity aspect is illustrated by the N-methyl-D-aspartate (NMDA) receptor agonists amantadine and memantine. With binding affinities of 20.25 ± 16.48 μM and 19.98 ± 3.08 μM, respectively (60), amantadine and memantine have a poor affinity for the σ site of NMDA receptor. Amantadine had a higher affinity for the phencyclidine (PCP) binding region on the receptor than memantine(10.5 ± 6.1 μM for amantadine and 0.54 ± 0.23 μM for memantine). It was observed that amantadine functioned at both the σ and PCP binding sites, whereas memantine exclusively acted at the PCP binding site, based on therapeutic doses of both drugs in the human brain (60). PET(Positron Emission Tomography) scans have been used to study receptor occupancy for various classes of drugs and clinical data for dopamine D1 and D2 receptors such as antipsychotics (61-63), histamine H1 receptors such as antidepressants (64), and serotonin 5-HT2 receptors such as antipsychotics (63) are available.

B. Change in Behavioral Symptoms and Clinical Ratings Scales : Unified Parkinson's Disease Rating Scale (UPDRS) (65), Hamilton Depression Rating Scale (HAM-D) (66), and Brief Psychiatric Rating Scale (BPRS) (67) respectively, are widely used by clinicians to aid with the diagnosis and progression of the diseases such as Parkinson's disease, depression, and psychosis, and to assess PD. In almost all clinical trials of symptomatic Alzheimer's (68), the Alzheimer's Disease Assessment Scale (ADAS) is used; however, various new rating scales have also been developed for Alzheimer's disease. According to a review published in 2010, only five of the 68 scales (68) matched the parameters for a robust multi-domain assessment of the disease.

Table 1 : Commonly used pharmacodynamic measures for CNS drugs andthe benefits and drawbacks of each method

Drug classification/ pharmacodynamic measure	Benefits	Drawbacks
I. Drugs for psychiatric and neurological conditions		
1. Receptor occupancy/binding affinity	+ Direct measure of a drug's efficacy + Can be used for drugs that interact with different receptor locations.	+ Discrepancies in values between in vitro and in vivo translation + Differences in species may result in complications
2. Behavioral symptom changes between animal and clinical rating scales	+ Are clinically understandable + Non-expensive	+ Difficult to make the interaction models and humans.

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	+ Can be used to track the progession of the illness + Non-invasive	+ Some illnesses such as Alzheimer's disease present with multiple ratings systems that may not always agree. This leads to problems with interpretation.
3. Neuroimaging markers information than subjective tests	+ Can provide more detailed + High-intensity magnetic fields exposure with fMRI.	+ PET scans are costly.
II. Anti-infectives		
1. Reduction of symptoms	+ PD measurement is simple.	+ Could be subjective. + PK/PD relationship can be difficult to interpret.
2. Bacterial count and viral load in CSF	+ Simple correlation	+ Invasive process that can be painful + Not enough information on whether CSF are comparable to brain tissue measurements.
3. HAND(HIV Associated Neurocognitive Disorder) scores	+ Non-invasive process + Comorbidities are explained using technique	+ Not clinically used research tool

C. Neuroimaging Markers : several distinct Pd measures are usually assessed utilizing Neuroimaging modalities. PET scans are utilised to figure out receptor abundance and occupancy profiles in vivo within the case of antidepressants (69), whereas functional magnetic resonance imaging (fMRI) provides data regarding changes in brain structure and substantia alba integrity.

D. PD Endpoints for Anti-Infectives : Time to mitigation of neurological symptoms like headache, disorientation, and muscle weakness, additional as decrease in antimicrobial load (e.g. bacterial count, HIV infectious agent RNA) inside the CSF are common PD endpoints. Antibiotics are accustomed treat central CNS infections based on their in vitro minimum inhibitory concentration (MIC) and IC_{50} (drug concentration that yields 50% inhibition of microbial growth). Similarly, ARVs are usually chosen for CNS action supported their in vitro IC_{50} values (70). Patients with HIV experience a spread of neurocognitive deficits, and neurocognitive check scores, just like the global Deficit Score (GDS), are planned as a PD measure to provide a baseline of neurocognitive impairment and to look at illness progression (71).

The following three sections examine last offered target site clinical pharmacology data for three illness states: psychosis/schizophrenia, Alzheimer's illness and neuro-HIV. additional information concerning the studies mentioned throughout this article may also be found in Table 2.

Table 2 : Antipsychotic medications, anti-therapies, antiAlzheimer's and antiretrovirals pharmacokinetic and pharmacodynamic measures in the CSF and brain tissue in human studies.

Authors Reference	Study Population	Sample size	Drug(s)	Parameters and Results
I. Psychosis				
Pharmacokinetics				

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Wode Helgodt (80)	Humans with a psychotic Disorder patients	44	Chlorpromazine	CSF and plasma samples were examined.Clinical benefits in with CSF drug concentrations more than 1 ng/mL and plasma drug concentrations larger than 40 ng/mL	
Kornhuber Et.al (72)	Postmortem brain tissue of humans treated With Haloperidol	11	Haloperidol	The concentrations in five brain areas were measured using Liquid chromatography. The drug concentrations were 10 times greater than the recommended serum concentrations for treating schizophrenia.Population PK analysis estimated elimination $t^{1/2}$ from brain tissue to be 6.8 days.	
Rimo´n et al. (81)	Humans with Chronic Schizophrenia	12	Haloperidol	CSF and serum concentrations 12 hours after a dosage were compared at steady-state. CSF levels were 4.3% of serum levels.	
Sampedro et al. (73)	Postmortem brain tissue	18	Amisulpiride, haloperidol, levomepromazine, norclozapine, olanzapine, paliperidone, quetiapine, risperidone, sulpiride, triapride, ziprasidone	The concentration of 17 antipsychotics in the prefrontal cortex was measured using liquid chromatography-tandem mass spectroscopy. In 10 samples, concentrations were found to be below the lower limit of quantification. High drug concentrations were found in certain samples, indicating drug overdose.	
Nyberg et.al (75)	Humans with a psychotic Disorder	48	Thioridazine	CSF and blood samples were collected in pairs. The exact time of collection is unknown. In CSF, the mean total concentration was 19.4 nmol/L and the free fraction was 49.1%.	
Pharmacodynamics					
Kim et al. (82)	Healthy Volunteers	18	Aripiprazole	At 3, 45, and 120 hours after the injection, PET was utilised to evaluate dopamine receptor	

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occupancy.
Based on PD modelling, the EC_{50} was 11.1 ng/mL.
PK/PD modelling revealed an EC_{50} of 8.63 ng/mL.

Yokoi et al. (61)	Healthy Volunteers	15	Aripiprazole	After two weeks of daily dosing, PET was used to demonstrate D2 and D3 occupancy. There was dose-dependent receptor occupancy ranging from 40% to 95%.
Farde et al. (62)	Humans with a dopamine receptor Psychiatric Disorder	14	Chlorpromazine, clozapine, flupentixol, haloperidol, melperone, perphenazine, pimozide, raclopride, sulpride, thioridazine, thioxanthene, trifluperazine Hydrochloride	PET was utilised to evaluate occupancy at steady-state, 6 hours after dosing 65–85 % D2 receptor occupancy across the 11 drugs.

Table 2continued

Authors Reference	Study Population	Sample size	Drug(s)	Parameters and results
Mamo Et al. (63)	Humans with Schizophrenia	16	Ziprasidone	After 3 weeks of trough treatment, PET was employed to evaluate dopamine and serotonin occupancy. At 5-HT2, occupancy was 76%, while at D2, it was 56%.
II. Alzheimer's disease				
Pharmacokinetics				
Mochida et al. (85)	Healthy women	4	^{11}C-Donepezil	Women were given 1 mg and 30 lg ^{11}C-Donepezil orally and had a PET scan 2.5 hours later. In the brain, the mean standardised unit value for mean intensity of pixels scanned was 0.9, showing that radioactivity was distributed evenly throughout the brain as it was all across the rest of the body.
Valis et al. (86)	Humans with Alzheimer's	16	Donepezil	The concentrations of donepezil in CSF were determined using liquid chromatography.

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	Disease				The concentration of CSF was higher at 24 h (7.54 ng/mL) than it was at 12 h (5.19 ng/mL). There is no accumulation in the plasma.
DarrehShori et al.	Humans with Alzheimer's Disease	104	Donepezil	(87)	Ellman's colorimetric assay was used to measure AChE in the CSF and blood. The exact moment of collection is unknown, although all of the patients were in a steady state. The concentrations in the CSF were 10 times lower than in the plasma. After a 5 mg dose, CSF AChE-S inhibition was 30–40%, and 45–55% after a 10 mg dose.
Kornhuber et al.	Humans with mild to Moderate Dementia	6	Memantine	(88)	In 4 patients, plasma and CSF were measured 2–3 hours after the dose. CSF concentrations were 0.05–0.3 µM, which was 50% lower than serum.
Rohrig and Hicks	Postmortem human brain tissue	1	Memantine	(89)	The concentration in brain tissue was 5.7 mg/kg, which was 2.7 times greater than the concentration in heart blood (2.1 µg/mL) and 6.9 times higher than the concentration in femoral blood (0.83 µg/mL).
Cutler et al.	Humans with Alzheimer's disease	18	Rivastigmine	(91)	Cmax in CSF was 2- to 4-fold lower than plasma, and Tmax in CSF was longer (1.4–3.8 h) than plasma (0.5–1.67 h).
	Pharmacodynamics				
Wattmo et al.	Humans with Alzheimer's Disease	84	Galantamine	(93)	ADAS-cog MMSE IADL There was no correlation between plasma concentrations and any of the PD parameters.
	III. Neuro-HIV				
	Pharmacokinetics				
Yilmaz et al.	HIV-positive Humans	1	Efavirenz	(37)	Drug concentrations were measured using liquid chromatography-tandem mass spectroscopy. Median plasma concentration was 3718 ng/mL, and 16.3 ng/mL in CSF. CSF penetration was 0.44% of plasma

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Table 2 continued

Authors Reference	Study	Sample size	Drug(s)	Parameters and results
Bumpus et al. (105)	Postmortem human brain tissue	21	Atazanavir, efavirenz, emtricitabine, lamivudine, lopinavir, tenofovir	Liquid chromatography was used to determine drug concentrations, which were then compared to previous CSF measurements. For lopinavir, concentrations varied across brain areas, with lopinavir concentrations being lower in cortical grey matter than in other regions (p = 0.01). Other medicines had little effect, and tenofovir had a larger quantity in brain tissue than in CSF.
Curley et al. (59)	Virtual cohort Of Humans Simulations	Not applicable/ 100 virtual	Efavirenz	The permeability-limited PBPK model was used to predict CNS distribution. Plasma, CSF, and brain tissue all had median Cmax values of 3184 ng/mL, 49.9 ng/mL, and 50,343 ng/mL, respectively. The ratio of brain tissue to plasma was 15.8.
Pharmacodynamics				
Smurzynski et al. (101)	HIV-positive Humans	2636	Combination ARV therapy	Better results on neuropsychiatric testing (NPZ3) were linked to a higher CPE score for more than 3 ARV treatment regimens. There is no link between regimens containing less than 3 ARVs.
Baker et al. (102)	HIV-positive Humans	64	Combination ARV therapy	The results of neuropsychiatric testing (NPZ4) had no correlation with CPE. There was no relationship between brain volumetric alterations and CPE.
Caniglia et al. (104)	HIV-positive Humans	61,938	Combination ARV therapy	'Intention-to-treat' hazard ratios of four neuro-AIDS disorders - high CPE was linked to an increased risk of dementia

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ADAS–Cog- Alzheimer's Disease Assessment Scale–cognitive subscale, MMSE- Mini-Mental State Examination, IADL- Instrumental Activities of Daily Living, CSF- Cerebrospinal fluid, PK- Pharmacokinetic, PD- Pharmacodynamic, PBPK- physiologically-based pharmacokinetics, PET- Positron Emission Tomography, EC_{50}- 50% effective concentration, AChE- acetylcholinesterase, C_{max}- maximum concentration, T_{max}- time to reach C_{max}, $t^{1/2}$- elimination half-life, ARV- antiretroviral, CPE- CNS Penetration Effectiveness

Clinical Pharmacokinetics and Pharmacodynamics of Antipsychotics in the CNS

There are now 21 FDA-approved first- and second-generation antipsychotics for the treatment of adult and pediatric psychosis, since chlorpromazine was approved over 60 years ago. Despite tremendous progress in the field, the heterogeneity in PD response required for efficacy, as well as the link to target site exposure, is a major area that these drugs have yet to fully address. There is also no clarity on what PK target measure should be used to correlate antipsychotic effectiveness.

Antipsychotic medications are known to easily penetrate the brain. For example, haloperidol is detected in brain tissue at 10- to 30-fold higher concentrations than in the serum (72). Antipsychotic concentrations in brain tissue have also been reported from autopsy tissue; a 2012 study of prefrontal cortex tissue from 18 human autopsy samples found high levels of several drugs, including olanzapine (33,378 ng/g) and quetiapine (16,769 ng/g) (73); however, such reports frequently lack supporting information, such as plasma concentrations and postmortem intervals. The scientists hypothesised that the extremely high concentrations of olanzapine and the other drugs were due to overdose because the concentrations ranged from undetectable (<2 ng/ g) to high. As a result, such studies may not provide accurate information on the therapeutic range of antipsychotics concentrations. Clinical brain PK for the newer antipsychotics aripiprazole, lurasidone, and perospirone is unknown (74); although, their high apparent volume of distribution of 400–6000 L (74) indicates extensive tissue distribution. CSF concentration may be predictive of unbound brain tissue PK (27) in the absence of brain tissue concentration data, though this has not been confirmed in humans. Antipsychotics enter the CSF (31) in large amounts, and historical estimates of total CSF:plasma protein-unbound concentration ratios for older drugs indicate that they bind to CSF proteins in significant amounts. For example, in a study of thioridazine in 48 patients, lumbar puncture was followed by venipuncture to obtain ratios of parent drug and metabolite in CSF versus plasma. The average total CSF:unbound plasma ratio of thioridazine was 6 and varied from 1.9 to 16.9 (75), while it is unclear if all patients in this study were in steady-state conditions or what the time of CSF and plasma sampling was in relation to the dose (75). According to the same study, the mean free fraction of thioridazine in the CSF was 49%, and the unbound concentration in the CSF was double that in plasma, probably due to passive thioridazine diffusion across the BBB. The unbound concentration of thioridazine in plasma and CSF (75) was shown to have a significant correlation ($p = 0.002$), suggesting that unbound concentrations in plasma might be employed as a surrogate for CSF concentrations or neuroleptic efficacy. A subsequent study examined plasma from 53 patients who had just started taking thioridazine 200 mg/day for the first time six times over the course of 2 weeks; however, this analysis found no link between thioridazine plasma concentrations and antipsychotic efficacy (76).

Drug flow transporter substrates (such as risperidone and P-gp affinity) might haven't any correlation between plasma and CSF concentrations. completely different efficacy correlates, like unbound CSF drug concentrations, need to be utilised in these cases. Recent PK/PD studies have evaluated the link between CSF concentration of antipychotics and receptor occupancy data (77,78). whereas antipsychotic CSF concentrations (e.g. chlorpromazine) (79,80) are sometimes correlative with efficacy, typically|this can be} often not forever the case due to problems in quantifying low CSF drug concentrations (e.g. haloperidol) (79,81). If there is metabolism to a moiety with antipsychotic activity, another potential confounder inside the association between drug concentration and efficacy develops. For example,9-hydroxyrisperidone (paliperidone), active part of risperidone, can be a marketed antipsychotic.

For antipsychotics, the connection of combined PK/PD modelling has been tested over PD alone. PET scans were conducted predose, 3, 4, 5, and 120 hours once aripiprazole was

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administered to eighteen patients in doses ranging from 2 to 30 mg (82). Due to delayed effect-site stabilization, there was hysteresis inside the connection between dopamine receptor occupancy and plasma concentrations. As a result of this, 50% effective concentration (EC_{50}) value varies depending on the sort of modelling used. The EC_{50} was 8.6 ng/mL (82) during a combined PK/PD analysis of anticipated effect-site concentration vs receptor occupancy, but it had been slightly higher (11.1 ng/mL) during a PD-only analysis due to hysteresis inflicting a shift inside the concentration–response slope. A combined PK/PD analysis produces more reliable estimates of activity and proper PD endpoints for medication with a discrepancy between the time course of measured plasma concentration and receptor occupancy (82, 83).

Clinical pharmacokinetics and Pharmacodynamics of medication accustomed Treat Alzheimer's within the CNS

Interpedine and verubecestat were the foremost recent treatment failures for Alzheimer's disease (84) in the months of September and November of 2017. A review of the clinical medicine of the presently authorized Alzheimers medications reveals varied plausible reasons for trial failure. Alzheimer's disease can be a chronic condition inside that deteriorating brain pathology could end up in altered drug concentrations in the brain. once evaluating PK results from healthy people or animal models, this can be troublesome. as an example, a recent PET scan analysis performed 2.5–3 h (time to reach higher concentration [Tmax]) once one oral dose of 1 mg or 30 µg ^{11}C-donepezil in four healthy women (85) disclosed that the mean standardised unit price for mean intensity of pixels imaged (SUV_{mean}) within the brain for every doses was 0.9, indicating associate virtually even distribution of emission within the brain. However, whereas obtaining multiple lower concentrations inside the CSF than plasma (86,87), larger concentrations inside the CSF were detected once 24h postdose compared to 12h postdose during a study with donepezil in presenile dementia patients. Typically this can be often probably to be as a result of P-gp supermolecule degradation within the progression of Alzheimer's (donepezil is a P-gp substrate), that lowers drug efflux from CSF (87). Given the P-gp location in the BBB and its perform within the flow of medication from brain tissue, one could expect donepezil to accumulate equally in Alzheimers patients' brain tissue, although typically this can be often unsure. The quality of surrogate PK measures and their relationship with target site concentrations is another issue to look at. The NMDA receptor antagonist memantine concentrations inside the CSF of 6 patients (0.05–0.3 µM) were 50% below serum concentrations (88), whereas the brain tissue concentration of memantine (5.7 mg/kg) was 2.7-fold above femoral blood concentration (2.1 µg/ml) and 6.9-fold above the femoral blood concentration (0.83 µg/ml) (89) during a single autopsy patient. Whereas the data is limited, memantine can be a basic component (pKa = 10.7) (88), and sequestering among acidic lysosomes via pH partitioning and lysosomal trapping might even be in charge of the drug's accumulated brain accumulation over CSF. Whereas clinical concentrations of the acetylcholinesterase (AChE) inhibitor rivastigmine (90) among the brain tissue remain unknown, continuous CSF sampling in 18 patients at steady state for up to 12 h postdose (91) in full view that rivastigmine had differential PK in plasma and CSF. CSF had a 2 to 4-fold lower most concentration (C_{max}) than plasma, and CSF had a extended T_{max} (1.4–3.8 h compared to 0.5–1.67 h).

The utility of PD measures in patients with Alzheimer's disease is little known. For example, an earlier review noted that using AChE activity measurements as an outcome measure can be difficult due to confounding by a variety of factors such as diet, concurrent medication, or the time of lumbar puncture (92), making the effect size of PK/ PD analyses more difficult to interpret. Furthermore, while some studies use plasma concentrations to predict treatment outcomes (93), plasma concentrations must first be verified as a suitable substitute for the target site.

Clinical Pharmacokinetics and Pharmacodynamics of Antiretrovirals in the CNS

In 2007, the HIV analysis medical specialty was changed (71) to produce data on the neurocognitive disorders induced by HIV, that square measure mentioned as HIV-associated neurocognitive disorders (HAND). Since then, the CNS has been referred to as an anatomical HIV (94-97) reservoir, capable of sustaining latent viral infection in phagocyte and glia cells within the brain. thus on progress our data of the treatment and so the chance of a cure for HIV within the CNS, it's necessary to know the PK of ARVs within the

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CNS and their relationship with neurocognition and latent reservoirs.

In the CSF, ARV PK has been thoroughly investigated, and the reader is directed to two reviews that summarise this topic (44,98). Letendre established a CNS Penetration Effectiveness (CPE) score that accounts for ARV efficacy and extent of penetration into the CNS (99), based on CSF PK measurements, physicochemical features of the drugs, and clinical utility. The scores range from 1 to 4, with 1 indicating the least effective (lowest CNS penetration) and 4 indicating the most effective (maximum CNS penetration) (99). In HIV patients (100), ARVs with a higher CPE score generate a greater reduction in viral load in the CSF; nevertheless, the relationship between CPE score and the degree of neurocognitive impairment in patients with HAND is inconsistent. While utilising agents with a higher CPE score was related with improved neurocognitive performance in certain studies (101), there were instances where a higher CPE was not associated with neurocognitive improvement (102), or when a higher CPE was associated with poorer functioning (103,104). Due to contradicting PK/PD results, one possibility is that the ARV concentration in brain tissue may be a better predictor of neurocognitive decline in patients with HAND; yet, clinical data on the correlation between CSF and the brain tissue concentrations of ARVs are insufficient. In a modest study by Bumpus and colleagues, the concentration of ARVs in subcompartmental brain tissue was evaluated in nine HIV-positive adults who died of AIDS (105). From necropsy samples, concentrations in the white matter, cortical grey matter, and globus pallidus regions of the brain were compared to historical CSF concentration data (105). For efavirenz, emtricitabine, atazanavir, and lamivudine, there was no difference in brain and CSF concentration; however, for tenofovir, the overall brain concentration of

206 ng/g was 37-fold greater than CSF. A protease inhibitor, lopinavir, was shown to be highly accumulated in white matter (>400 ng/g) than in other brain regions (<25 ng/g). A new in silico model (59) predicted that efavirenz accumulates in brain tissue, with a median tissue to plasma penetration ratio of 15.8. According to data recently published in 12 non-human primates (106), tenofovir, emtricitabine, efavirenz, raltegravir, maraviroc, and atazanavir all attained higher total concentrations in brain tissue than in CSF at trough. The highest brain tissue to CSF concentration ratio (769-fold) was found for efavirenz, while the brain tissue to plasma penetration ratio ranged from 3 to 5.7, indicating accumulation of efavirenz. Because data on patient adherence was not available for Bumpus et al., study, and comparisons between brain tissue and CSF concentrations were based on historical CSF estimates, low adherence to an ARV regimen before death could explain why efavirenz concentrations were equivalent to CSF measurements and much lower in these samples than in non-human primates.

PK/PD correlations as they relate to the establishment of latent reservoirs in target cells of the brain tissue are an important area for future research. With advancements in MS imaging, this technique may be able to identify particular ARV distribution patterns in the brain (20), which could lead to differential viral proliferation or latency if ARV coverage is insufficient. Another area of research is providing an effective range of intracellular concentration for preventing HIV cellular infection without causing CNS toxicity (107).

PK/PD Optimization

■ **Biomarker Investigation**

Abnormal protein aggregation can induce cognitive impairment or dementia (108) in Alzheimer's disease. Protein accumulation processes frequently begin prior to clinical manifestations. As a result, it's critical to look for quantifiable proteins or biomarkers in the CSF or blood for diagnosis. According to a recent study, biomarkers may also be useful as PD endpoints, with amyloid and tau in the CSF being routinely employed biomarker outcome measures in ongoing Alzheimer's disease (109) clinical trials. The efficacy of these measures is based on the stability of these biomarkers over time and significant variations in concentrations achieved between patients with Alzheimer's disease and healthy volunteers, as previously proven. Kielbasa and Lobo recently proved the value of biomarkers in the development of antidepressant drugs. The antidepressants atomoxetine, duloxetine, and edivoxetine's plasma PK concentrations were modeled against the CSF concentration of 3,4-dihydroxyphenylglycol (DHPG) (111), the deaminated form of norepinephrine, as a biomarker in an indirect response analysis. All antidepressants had a maximum inhibition rate of DHPG formation (I_{max}) of 33–37% in plasma, with edivoxetine being the most potent; however, in CSF, I_{max} was substantially higher for edivoxetine (75%) compared to atomoxetine (53%) and duloxetine

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(38%). Further clinical research into such biomarkers may contribute in the discovery of novel drug candidates.

To prevent confounding with subjective psychiatric tests, innovative biomarkers could be beneficial in the field of neuro-HIV as a surrogate measure for neurocognitive impairment (112). Although there have been no clinical studies evaluating the correlation of ARV and biomarker concentrations in HIV patients, however, neurofilament light chain (NFL) has shown promise as a biomarker related to HAND. Biomarkers should also be explored as a surrogate for the development of a latent HIV reservoir in the brain (113).

■ Simulation and Modeling

To predict drug disposition in the brain, several modelling tools have been developed. Using in vitro and animal data, both a top-down approach (population PK modeling) (78) and a bottom-up approach (physiologically-based PK [PBPK] modeling) (26, 77, 114, 115) have been used to estimate the brain penetration of various drugs in humans. Gaohua and colleagues recently introduced a PBPK model that included four additional brain (26) compartments: brain blood, brain mass, and cranial and spinal CSF. The model worked well for describing the anatomy and physiology of the brain, as well as passive and active transport pathways across the BBB. The model was used to simulate several scenarios that mimicked transporter-mediated processes and CSF turnover, and it was validated using measured clinical concentrations and in vitro data for phenytoin and paracetamol. The human brain and CSF PK of nine different drugs, including antipsychotics and antidepressants (116), was predicted using a recently developed generic PBPK model that incorporated five CSF compartments, including extravascular drainage from CSF as well as intracellular and extracellular brain compartments. Such approaches will vastly increase our knowledge of CNS target site approximations in humans. Incorporating both the PK profile and the concentration and effect of endogenous drugs into modelling techniques improves the accuracy of the results. For example, using plasma and CSF concentrations from the cisterna magna of two novel β-secretase 1 (BACE-1) inhibitors with β-amyloid and secreted amyloid precursor protein biomarkers (117), a mechanistic monkey PK/PD model was developed. Using in vitro cellular inhibition and enzyme activity, as well as drug concentration data, this model may predict in vivo BACE-1 inhibition and the effect on amyloid precursor processing by BACE-1 inhibitors.

■ Preclinical Models to PK/PD Translation

Developing novel animal models for CNS research could help researchers better understand clinical PK/PD issues such as the relationship between effect-site drug concentrations and novel biomarkers, as well as reveal hidden targets. Several neurobehavioral disorders, including depression, Parkinson's disease, and attention deficit hyperactivity disorder (ADHD) (118), have been studied using zebrafish models. They overtake typical laboratory species like rodents in terms of cost and genetic manipulation, and they possess a high degree of genetic and physiologic homology with mammals (119). Novel rodent models for pediatric epilepsy (120) and CNS involvement in HIV infection (121) have also been explored.

The clinical usefulness of existing animal models must be carefully investigated. For example, some animals may lack receptors or drug targets that are available in humans. Drug metabolising enzymes and transporters may be expressed or active differently among different animal models. Terasaki and colleagues used quantitative targeted absolute proteomics (QTAP) to measure the quantities of transporter proteins on the BBB of numerous species, including humans (50,122), and detected interspecies variations in several major transporters. For example, humans have a higher absolute concentration of BCRP (fmol/μg of protein) than mice, but mice have higher absolute concentrations of P-gp, organic anion transporting polypeptide 1A2 (OATP1A2), MRP4, and OAT3. Similarly, absolute transporter concentrations in cynomolgus monkeys resemble those in humans more closely than in mice. Because multiple transporters are involved in drug uptake and efflux across the BBB, the association between transporter expression/activity and PK in the CNS is not straightforward. As a result, while differences in transporter activity at the BBB are not currently taken into consideration in allometry, models that account for differential transporter activity between species in the CNS are needed to identify whether this requires alterations in the human dose.

II. CONCLUSIONS

For neuroactive drug development, understanding drug penetration and effect at

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multiple CNS locations is critical. Presently, antipsychotics, Alzheimer's medications, and antiinfectives all have information on drug distribution in the brain and CSF, but the interaction between drug concentration and effect is still unknown in these areas. Integrating PK/PD information for CNS drugs would allow for better first-in-human dose prediction and lessen the attrition rate in CNS drug development. Better use of methods like biomarker identification and modelling can help pave the way for a more rigorous explanation of clinical brain PK/PD in support of this.

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