**Pharmacokinetics-Pharmacodynamics of Antifungal Agents in the Central Nervous System**

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**Abstract**

**Introduction**

Mortality from invasive fungal disease involving the central nervous system (CNS) is excessive. Achieving therapeutic drug concentrations at the site of infection within the CNS is always difficult and its evaluation is complex due to anatomical barriers and variable pathophysiological lesions.

**Areas covered**

This review provides an updated summary of the CNS PK of antifungal therapies. It considers factors that influence the success of antifungal regimens for CNS infection as well as preclinical and clinical data that quantify antifungal pharmacokinetics (PK) in the CNS. Furthermore, it presents state-of-the-art technologies to enhance the clinical use of existing antifungal drugs, and introduces novel antifungal drugs in development.

**Expert opinion**

The antifungal drugs currently available are either suboptimal, or are being used suboptimally, for CNS disease. Therapeutic drug monitoring is mandatory to enhance their effectiveness. Novel drugs in development may offer more efficacious options. In all cases, contemporary technologies to assess CNS PK offer the opportunity to enhance our understanding and use of antifungal drugs for CNS fungal disease.

**Keywords:**

Antifungal, central nervous system, cerebrospinal fluid, brain, pharmacokinetics, distribution.

**Introduction**

Mortality from invasive fungal diseases involving the central nervous system (CNS) frequently exceeds 50% (1). There are unique challenges for drug penetration within the CNS. The blood-brain barrier and blood-cerebrospinal fluid barrier create an obstacle for free diffusion of compounds into the CNS. Hence, plasma drug concentrations are not reliable surrogates for concentrations within diseased areas within the brain (2). Complex pathophysiology and nonspecific clinical presentations often lead to a late diagnosis of CNS mycoses and this further compromises pharmacological treatment. This review provides a summary of current knowledge of the CNS pharmacokinetics (PK) of antifungal therapies.

**1. CNS PK of antifungal drugs**

The CNS is comprised of multiple sub-compartments that include the cerebrospinal fluid (CSF), cerebral parenchyma, ventricles and meninges (3). These areas are pharmacologically distinct. A number issues are pertinent for a complete understanding of the potential utility of an antifungal agent for the treatment of CNS mycoses. First, pathological changes within the CNS resulting from fungal invasion; second, physicochemical drug properties that influence the extent of partitioning into the CNS and areas of diseased tissue; and finally, PK variability.

**1.1 Pathophysiology of CNS fungal infections**

Fungi vary considerably in the extent to which they are neurotropic. For some pathogens, such as *Cryptococcus neoformans* and *Cladophiolophra*, involvement of the CNS is so characteristic that it must be actively excluded if a diagnosis is established from a non-CNS site. For others, such as *Aspergillus* spp., CNS involvement is well characterised but is not invariably present. In addition, involvement of the CNS may depend on the host. For example, hematogenous *Candida* meningoencephalitis (HCME) is a disease that is characteristic of premature neonates, but highly unusual in adults. Table 1 summarises the considerable pathophysiological differences between CNS mycoses.

The nature and extent of underlying immunological deficits also has an important impact on patterns of infection and the cadence of clinical disease. For example, profoundly immunosuppressed patients with invasive CNS aspergillosis often present with a stroke-like illness resulting from cerebral infarction. This results from invasion and thrombosis of cerebral arteries by *Aspergillus* spp. In contrast, patients with chronic sinus aspergillosis may develop CNS disease via direct hyphal invasion through the lamina papyracea. These patients often only have mild immunological deficits (e.g. diabetes, low dose corticosteroid treatment) with clinical signs and symptoms that develop over many months. The histopathology of these two diseases is distinct. Cerebrovascular aspergillosis is associated with a paucity of inflammation, infarction and cerebral haemorrhage. In contrast, chronic *Aspergillus* sinusitis is associated with florid pyogranulomatous inflammation.

Systemic physiological changes associated with CNS mycoses may also have an impact on the PK of antifungal drugs. Systemic infection alters cerebral blood flow, blood and tissue pH and intra- and extra-cellular fluid volumes, all of which exert profound influence on systemic PK and drug penetration into the CNS (4-6). Meningeal inflammation may increase the concentration of antimicrobial agents in the CSF by over 10-fold (7). In some cases the blood-brain barrier (BBB) is completely disrupted, allowing unfettered access of the drug to the pathogen.

**1.2 Physicochemical properties of the drug**

The CNS is protected from many circulating xenobiotics by the presence of blood tissue barriers that limit diffusion from the endovascular compartment into the CSF and brain parenchyma. A summary of antifungal drug characteristics that influence the degree to which drugs partition across the BBB and the blood-cerebrospinal fluid barrier (BCSFB) is presented in Table 2. Tight cellular connections in the BBB and BCSFB (approximately 2 nm) prevent the passive diffusion of large compounds into the CNS (3). Efficient diffusion is possible only to an upper molecular weight limit of 300–400 g/mol (8).

The lipophilicity of compounds influences the extent of CNS partitioning (4, 9). Drug lipophilicity is quantified as the partition coefficient (LogP) between aqueous and lipophilic phases (usually determined with water and octanol). A more physiologically relevant expression of lipophilicity is LogD, which accounts for the fact that many drugs are ionised at physiological pH. Compounds that are not ionized at physiological pH have the greatest lipophilicity and better penetrate the BBB and BCSFB (4, 10). LogP and LogD values of approximately 2–4 are associated with optimal BBB penetration (10, 11). Protein binding also influences the degree of partitioning into the CNS. Passive diffusion of molecules into the CNS depends on a concentration gradient between unbound drug in the plasma and that in the brain (12). Protein binding is often inversely correlated with LogP.

Finally, efflux pumps in the BBB and BCSFB may remove compounds from the CNS via an energy-dependent process (3, 4). P-glycoprotein is a membrane-bound efflux pump with an affinity for lipophilic molecules. Some triazole agents (itraconazole, posaconazole and isavuconazole (13)) are substrates for P glycoprotein, while other triazoles (fluconazole and voriconazole) are not. There is conflicting evidence regarding the role of P-glycoprotein in the efflux of amphotericin B from the CNS (14, 15).

**1.3 PK variability**

Several antifungal drugs exhibit non-linear and/or highly variable PK. The PK of itraconazole, voriconazole, posaconazole and flucytosine are sufficiently variable to warrant routine therapeutic drug monitoring in the context of invasive fungal disease, regardless of whether there is CNS involvement (16). This variability is inevitably more extreme when penetration into the CNS is considered, since it is amplified by barriers such as the BBB and BCSFB as well as pathological changes within the CNS itself. Thus, while plasma drug concentrations are highly variable, CNS drug concentrations likely more so, and the former are an unreliable surrogate for the latter.

The prediction and evaluation of the CNS PK of antifungals is thereby complex. Inter- and intra-individual variability in each contributing factor extends this complexity (4, 16). Ideally, the information required to establish robust pharmacokinetic-pharmacodynamic (PK-PD) targets at the site of infection in the CNS includes all of the points listed in Box 1. Using this information, data can be modelled using a variety of approaches to predict human CNS PK. These approaches can broadly be categorized into classical population PK modelling (the ‘top-down’ approach) and physiologically based PK (PBPK) modelling (the ‘bottom-up’ approach) (17). For example, population PK models have been constructed from preclinical investigations of micafungin (18) and anidulafungin (19), with Monte Carlo simulation used to bridge the results to neonatal populations at risk of *Candida* meningoencephalitis. Whilst PBPK models describing the CNS PK of antifungals are scarce, examples of the application of PK modelling to the prediction of CNS PK exist in the general pharmacology literature. A multi-compartmental PBPK model has been shown to adequately describe the PK profiles of nine structurally diverse drugs in the plasma, brain extracellular fluid and CSF of rats (20). The model was additionally able to predict human concentration-time profiles in brain compartments (20, 21). PBPK models can also predict the influence of genetic polymorphisms on CNS PK and PD (22).

**2. Evaluation of data relating to the CNS PK of antifungal drugs**

Studies of the CNS penetration of antifungal drugs in humans are often limited. Firstly, drug concentrations in CSF, which is the only readily available biological matrix in clinical studies, may not be representative of concentrations in other CNS sub-compartments. Secondly, studies tend to report point estimates of CNS drug partitioning rather than the trend of drug concentrations over time (i.e. area under the concentration-time curve; AUC) in the plasma and the CNS.

For obvious ethical and technical reasons, quantification of drug in the CNS using conventional methods such as collecting samples of tissue for liquid chromatography-mass spectrometry (LC-MS) or bioassay in clinical studies is challenging (see, for example, (23, 24)). Achieving this at several time points throughout the dosing interval is even more so (2). Information of this type is invariably derived from preclinical models. Using more contemporary technologies, clinically relevant estimation of CNS drug partitioning is becoming easier. Examples of these technologies are intracerebral microdialysis (12) and non-invasive imaging techniques such as positron emission tomography (PET) (25) and magnetic resonance (MR) imaging (26). Key findings that preclinical and clinical studies have provided are presented in the following section of this review, alongside a review of their clinical application.

1. **The triazoles**

Fluconazole

Fluconazole has physicochemical properties that enable it to traverse the BBB and BCSFB (Table 2). The equilibration of fluconazole between plasma and cerebral extracellular fluid occurs rapidly and is independent of dose (27). Relatively high concentrations are found in the CSF. PK studies in rabbits and adult Rhesus monkeys demonstrated mean CSF:plasma AUC ratios of 0.84 and 0.86 respectively, with a long half-life in the CSF of approximately 27 hours (28, 29).

Early human CNS PK studies using traditional bioassay or LC-MS reported a range of partition ratios from 0.52 – 0.89 (23, 30). Subsequently, a combined approach using positron emission tomography (PET) scanning and plasma PK sampling demonstrated an approximately uniform distribution of fluconazole in the healthy human brain, with a brain:plasma penetration ratio of 1.31 (25). This was corroborated by an analysis of 4 patients undergoing brain tumour excision in whom healthy brain parenchyma was also removed. In these patients, HPLC demonstrated a mean healthy brain:plasma fluconazole ratio of 1.33 (24).

A fluconazole regimen of 1200mg/day for the 2 week induction phase of treatment for cryptococcal meningoencephalitis is recommended if polyenes are unavailable (31). This dosage is more rapidly fungicidal than 800mg/day (32). The addition of flucytosine to fluconazole is recommended because it reduces mortality (33). These oral regimens for cryptococcal meningitis are pragmatic recommendations given the unavailability of polyenes in many regions with a high burden of cryptococcal meningitis, despite broad agreement that amphotericin B deoxycholate is currently the agent of choice (34, 35). Fluconazole is also used at dosages of 400-1200mg/day to treat CNS infection with *Coccidioides* (36, 37).

Itraconazole

Itraconazole concentrations in CSF are negligible, with CSF:plasma concentration ratios of <0.002 to 0.12 in preclinical models (2, 38-40). Even in the setting of infection and inflammation, itraconazole is undetectable in rabbit CSF (40). Low CSF concentrations have been attributed to rapid binding to red blood cells and circulating plasma proteins, inhibiting BCSFB penetration (41). However, murine experiments have demonstrated rapid, dose-dependent penetration and linear accumulation of itraconazole in brain tissue up to 8 minutes post-dose, implying that it does cross the BBB (42). In a murine model of CNS histoplasmosis, itraconazole levels were almost universally undetectable in brain tissue 3 hours post-dose (43). Itraconazole has a strong affinity for P-glycoprotein, which results in rapid efflux from the CNS such that half-life in cerebral tissue may be considerably shorter than that in plasma (0.4h versus 5h, respectively) (42, 44).

The efficacy of itraconazole for the treatment of cryptococcal meningoencephalitis (40), CNS aspergillosis (45) and *Coccidioides* meningitis (38) is well established in laboratory animal models. The apparent discrepancy between CNS drug concentrations and therapeutic efficacy of itraconazole in CNS fungal infections may be due to a combination of higher drug concentrations in the brain tissue than in CSF, and the relatively low minimum inhibitory concentration of itraconazole against target fungi such as *Candida* (46) and *Histoplasma* (43). In addition, the pharmacologically active metabolite of itraconazole, hydroxyl-itraconazole, has been detected in brain parenchyma with greater consistency than has the parent drug (43). In humans, itraconazole is effective for primary prophylaxis of cryptococcal meningitis, with a relative risk of incident cryptococcal meningitis of 0.12 (95% confidence interval, 0.03, 0.51) versus placebo (47). Inconsistent success rates have been reported for the treatment of cryptococcal meningitis with itraconazole. The treatment of 6 patients with 200mg/day resulted in therapeutic failure (deterioration or death) in 3 (50%) (48). Of 20 evaluable patients with culture- or antigen-diagnosed cryptococcal meningitis treated with itraconazole 400mg/day, 13 (65%) achieved clinical and microbiological cure (49). Cryptococcal meningitis progressed in 2 patients receiving itraconazole 600mg/day (50). After recovery from cryptococcal meningitis, maintenance therapy with itraconazole is associated with significantly more relapses of cryptococcal meningitis compared with fluconazole (51).

Itraconazole is not included in current cryptococcal meningitis treatment guidelines from the World Health Organisation (31), though it may be used as prophylaxis against cryptococcal meningitis, particularly in patients with CD4 counts <100 cells/µL (52). Despite the availability of newer antifungal agents, the oral bioavailability and broad spectrum of antifungal activity of itraconazole mean that it remains a useful drug for the management of invasive mycoses worldwide (53). It is recommended as second-line therapy for CNS infection with *Candida*, *Aspergillus, Histoplasma* and *Coccidioides* spp. (36).

Voriconazole

Voriconazole has a relatively low molecular weight (349 g/mol), is moderately lipophilic and is a weak substrate for P-gp (Table 1). It exhibits good CNS penetration. In guinea pigs, 10 mg/kg voriconazole penetrates the BBB into brain parenchyma rapidly, reaching peak concentrations of 6.8 µg/g and 2.7 µg/g 15 minutes and 1 hour post dose, respectively (54). The CSF:plasma ratio in healthy animals is 0.68 (54).

Studies in humans have demonstrated that voriconazole penetrates the BBB and BCSFB, including into brain parenchyma (55) and cerebral abscesses (56). A wide range of concentrations in human CSF range have been reported, from 0.08 to 3.93 micrograms/mL in the initial 10 h post voriconazole administration. CSF:plasma ratios are 0.22-1.0 (54). This wide range is likely due to the extensive PK variability of voriconazole (16, 57-61). In contrast to CSF, concentrations in the brain are ≥2-fold plasma levels (26). A study that used fluorine-19 MR spectroscopy reported steady-state brain:plasma voriconazole concentration ratios of 3.0 (90% CI 1.9 – 4.7) pre-dose and 1.9 (90% CI 1.2 – 3.0) post-dose in healthy adult men (26).

Voriconazole exhibits potent activity against *Aspergillus* spp. (Table 2) and is a standard-of-care for CNS aspergillosis (62). It is also indicated for CNS infection with *Scedosporium apiospermum* complex and fluconazole-resistant *Candida* spp. (Table 2), the latter being primarily confined to the neonatal setting.

Posaconazole

Posaconazole is structurally similar to itraconazole, but less lipophilic (2). It is both a substrate and an inhibitor of P-gp *in vitro* (63), although polymorphisms of P-gp do not affect posaconazole AUC *in vivo* (64). The oral suspension of posaconazole exhibits variable bioavailability and inconsistent PK (65, 66). Alternative tablet, capsule and intravenous formulations have been partly successful in addressing these issues (67-71). Based on the physicochemical properties of posaconazole, poor CNS penetration is expected (Table 2). In murine models of infection with *C. gattii* and *Fonseca monophora*, mean posaconazole brain:serum concentration ratios are < 0.54 with dosages of 10-20 mg/kg. These increase to 0.69-0.84 following dosages of 40 mg/kg (72, 73).

Human CNS PK data for posaconazole is sparse and limited to case reports. The CSF:plasma concentration ratios range from 0 (single CSF sample analysed in each case) (74, 75) to <0.009 (in 6 serial CSF samples) (76) in patients without significant meningeal inflammation. In patients with bacterial meningitis and cerebral fungal infection, CSF:plasma posaconazole concentration ratios as high as 0.44 and 2.37 are reported, suggesting that meningeal inflammation may improve CNS penetration (75). Posaconazole penetrates into fungal brain abscesses (75).

Posaconazole is not recommended as a first-line agent for any fungal infection of the CNS. Posaconazole is indicated as second line therapy for coccidioidomycosis (77), and mucormycosis (78) and as salvage therapy for invasive aspergillosis (79, 80) and histoplasmosis (81) (Table 2, (36)).

Isavuconazole

Isavuconazole is structurally similar to fluconazole and voriconazole, although it has a higher molecular weight and LogD value (Table 2). Studies in healthy rats suggest that the mean brain:plasma isavuconazole concentration ratio is 1.8 (82). Following administration of 14C-labeled isavuconazonium sulphate, radioactivity in brain tissue increases in proportion with radioactivity in blood, and reaches a maximum at 2h post-dose before declining to undetectable levels 24h post-dose (82). Similar CNS penetration is evident in a murine model of cryptococcal meningitis with brain:plasma AUC ratios of approximately 1.35 (83).

Data describing the PK of isavuconazole in the human CNS are scant. However, of 27 patients with CNS fungal infection with aspergillosis, cryptococcosis or mucorales treated with isavuconazole, survival at 6 months was 50% (84).

**3. Polyenes**

There are several formulations of amphotericin B (AmB) available for clinical use: amphotericin B deoxycholate (DAmB), liposomal amphotericin B (LAmB), amphotericin B lipid complex (ABLC) and amphotericin B colloidal dispersion (ABCD) (36, 85). ABCD is no longer marketed in many countries. All approved formulations are administered intravenously. The large molecular weight of AmB is likely to be the primary reason for its relatively poor CNS penetration (86, 87) (Table 2). An *in vitro* model of the BBB demonstrated that permeability to both LAmB and DAmB was significantly increased in response to enlargement of endothelial cell junctions via exposure to either tumour necrosis factor alpha or lipopolysaccharide (88). In addition, AmB may be a substrate for efflux pumps at the BBB (14, 15).

In a rabbit model of CNS *C. albicans* infection, CSF:plasma ratios ≤ 0.02 and brain:plasma ratios ≤ 0.27 were reported for all four AmB formulations (86). The CNS penetration ratios of all formulations are higher in the setting of CNS infection compared with healthy brain tissue (maximum AmB CSF:plasma ratio 0.03 with ABCD and ABLC; maximum brain:plasma ratio 0.11 with ABCD) (86).

LAmB has the lowest CNS penetration ratio of all formulations despite its smaller particle size (Table 2). However, the PK of LAmB is characterised by serum concentrations 30-fold greater than other AmB formulations. Thus, the absolute concentration of AmB in brain tissue following LAmB administration is ultimately several times higher than following administration of the other formulations (3, 86). An immunohistochemistry study of LAmB in brain sections of mice with cryptococcal meningitis revealed that amphotericin B was present in both intravascular and perivascular spaces (89). The proportion of liposome-associated AmB versus free drug in brain tissue after administration of LAmB is unknown.

After as few as 3 dosages of DAmB, there is prolonged mean residence time of AmB in rabbit brain tissue despite negligible concentrations in CSF (90). In human studies of LAmB PK, CSF:plasma concentration ratios of 0.001 have been reported (91). Autopsy studies have found concentrations of AmB in human cerebral cortex to be lower than those in liver, spleen, kidney and lung, with no significant difference between the concentrations detected after administration of LAmB and ABCD (92).

Despite consistent reports of low or undetectable CNS concentrations of AmB, its efficacy against many CNS mycoses in humans, including cryptococcal meningitis, is well established (93-96). A likely explanation for this is that amphotericin B concentrations are high in the meninges where the yeast predominantly resides. Hence there is co-localisation of drug and pathogen, although to date this has been difficult to verify.

The clinical utility of polyenes in regions of the world with high burden of fungal CNS infection, in particular cryptococcal meningitis but also CNS histoplasmosis, murcomycosis, sporotrichosis and trichosporonosis, is limited by the requirement for intravenous administration, prolonged inpatient admission and close monitoring for toxicity.

**4. Flucytosine**

Flucytosine has several attributes that are conducive to high CNS penetration including low molecular weight, low protein binding and polarity (Table 2). High dose-proportional concentrations are consistently recorded in both brain parenchyma (97) and CSF, with CSF:plasma ratios 0.74 - 0.84 in humans from 1-2 hours after dosing (98, 99). The activity of flucytosine appears to be time- rather than concentration-dependent (98, 100, 101).

Flucytosine is active against *Cryptococcus* spp., most *Candida* species and has some activity against *Aspergillus* species (16, 31). Its use in monotherapy is widely thought to be precluded by the development of resistance, which has been consistently documented *in vitro* (102-104). While reports on the clinical use of flucytosine monotherapy are sparse, a case series of 23 patients with cryptococcal meningitis treated with flucytosine monotherapy reported that of 12 patients who failed therapy, the development of resistance was implicated in 50% (105).

In practice, flucytosine is used in combination therapy. In this setting, flucytosine is vital to secure optimal outcomes in cryptococcal meningitis: Trials comparing DAmB alone with DAmB in combination with either flucytosine or fluconazole have demonstrated superior outcomes in the flucytosine combination arms, in terms of CSF sterilisation (106, 107) and mortality (106). Its addition to AmB facilitates reduced treatment durations for cryptococcal meningitis (108). 5FC may also have a role in HCME, where its addition to AmB is at least additive and may be synergistic in preclinical models (109, 110). A retrospective study of humans with *Candida* meningitis reported survival in 15 of 17 patients treated with the combination of flucytosine and AmB (111). This combination is recommended for *Candida* meningitis in children (112) though caution is advised because of the risk of toxicity, particularly in premature neonates (113).

**5. Echinocandins**

Caspofungin, micafungin and anidulafungin do not extensively partition into the CNS due to their large molecular weight and high level of protein binding (Table 2, (114)). Micafungin achieves brain:plasma concentration ratios <0.01 at doses of 0.5 – 2mg/kg in healthy rabbits (115). In rabbits with HCME, micafungin penetrates all CNS compartments (cerebrum, cerebellum, spinal cord, meninges and CSF) in a dose-dependent fashion, but only with dosages >2mg/kg (18). The presence of CNS infection and inflammation does not increase the CNS penetration of micafungin (18). Brain tissue concentrations of anidulafungin also increase in a dose-dependent manner, achieving brain:plasma ratios of 0.10-0.12 at doses of 0.5-10 mg/kg in neutropenic rabbits with disseminated *C. albicans* infection (116). Studies of radiolabelled caspofungin at dosages of 1-2mg/kg demonstrate brain:plasma penetration ratios of <0.09 in rodents (117). For all three echinocandins, penetration into each of lung, liver, spleen and kidney exceeds that into brain tissue (115-117).

Human CNS PK data for echinocandins is limited to case reports. A patient with a cerebral mass treated with micafungin at a dosage of 100mg q24h achieved a brain:plasma concentration ratio of 0.18, 23 hours after dosing (118). A patient dosed with micafungin 300 mg/day for CNS aspergillosis achieved a CSF:plasma ratio of 0.0005 (119). A case report of a patient treated for *Candida* endocarditis describes the development of new cerebral abscesses during caspofungin treatment (120).

There is experimental evidence from well characterised rabbit models of HCME that anidulafungin and micafungin are potentially effective agents (18, 19). The weight-based dosages predicted for efficacy from PK-PD bridging studies are in excess of those recommended in adults for invasive candidiasis. This finding promoted further clinical studies of micafungin that included dosages up to 15 mg/kg. The European Society of Clinical Microbiology and Infectious Diseases recommends that a dosage of 10mg/kg is considered for neonatal HCME (18). Echinocandins may also be considered as an adjunct to other first-line antifungal agents for the treatment of CNS infection caused by *Aspergillus* spp., *Scedosporium apiospermum* complexand *Lemontospora* *prolificans*. (Table 1).

**6. Expert opinion**

The antifungal drugs currently available are either suboptimal, or are being used suboptimally, for CNS disease. However, the technological and scientific capacity to improve this situation exists.

Reformulation of drugs can improve their distribution through the BBB and BCSFB. In particular, nanoparticulate drug formulations offer promise in terms of CNS distribution. These submicrometer units may improve drug transport across the BBB by transiently increasing BBB permeability or by internalizing into brain capillary endothelial cells and thus traversing the intact BBB transvascularly (121, 122). These concepts and a description of specific carriers are presented elsewhere (123, 124). A number of examples of the exploration of nanostructured antifungal drug preparations exist. A nanosuspension formulation of amphotericin B increased AmB concentrations in mouse brains by a factor of 2.5 – 4.25 relative to LAmB (128). Amphotericin B-containing micelles, modified using a ligand of low-density lipoprotein receptor-related protein present on the BBB, have shown better BBB penetration than unmodified micelles or amphotericin B deoxycholate both *in vitro* and *in vivo* (125). Nanostructured liposomes can increase itraconazole concentrations by 2-fold in mouse brains (129). These chemical modifications represent potential avenues to maximise the utility of currently available antifungal drugs for CNS infections.

Therapeutic drug monitoring (TDM) is a standard of care for the triazoles and 5FC regardless of the site of infection (130, 131). For CNS mycoses, antifungal TDM is even more critical to ensure adequate concentration at the effect site. Targets for TDM for efficacy are generally based on non-CNS disease. Hence, clinicians must use their judgement as to which target to aim for in TDM. From a pragmatic perspective, aiming for higher concentrations within the therapeutic range is a reasonable strategy (rather than being reassured by concentrations that are just within the therapeutic range).

**Novel antifungal drugs with potential for use as CNS agents**

Several promising new antifungal compounds are under investigation and may hold promise as treatments for CNS disease. Viamet Pharmaceuticals (Durham, North Carolina, USA) have developed VT-1129, a quaternary azole that is efficacious in murine models of cryptococcal meningitis (132) and systemic candidiasis (133). Cidara Therapeutics (San Diego, CA, USA) are developing a novel semisynthetic echinocandin, CD101. CD101 is active against *Candida* and *Aspergillus* spp.(134), but in preclinical models displays tissue distribution patterns in keeping with currently available echinocandins, penetrating poorly into brain parenchyma (135).

F901318 (F2G limited, Eccles, UK) is the leading compound in a novel class of antifungals, the orotomides, which block fungal pyrimidine synthesis (136). F901318 is active against *Aspergillus* spp., including resistant strains (137), as well as *Penicillium* spp., Coccidiodes immitis, H. capsulatum, Blastomyces dermatitidis, Fusarium spp., and the difficult-to-treat Scedosporium spp. (136). F901318 is detectable in brain tissue after administration to mice (136). Amplyx Pharmaceuticals (San Diego, CA, USA) have developed a novel antifungal agent, APX001, which inhibits a glycosylphosphatidylinositol-anchored fungal wall transfer protein (138). APX001 exhibits highly selective in vitro antifungal activity against *Candida* spp*.*, including strains resistant to fluconazole, Aspergillus fumigatus, A. niger, A. flavus, A. terreus, Fusarium, Pseudallescheria boydii, and S. prolificans (139, 140)*.* In a murine model of disseminated *C. auris* infection, APX001 improves survival by up to 2-fold relative to anidulafungin, with demonstrable PD effect in brain tissue (138). APX001 was granted orphan drug status by the US Food and Drug Administration in 2016 (141). Another novel first-in-class antifungal agent is SCY-078 (SCYNEXIS, Jersey City, New Jersey). SCY-078 is a semisynthetic derivative of enfumafungin and the only compound in the triterpene class of antifungals (142). It is a potent inhibitor of β-(1,3)-D-glucan synthesis in fungal cell walls and demonstrates broad spectrum activity against *Candida* spp. (143), including *C. auris* (144) and *Aspergillus* spp. (145) *in vitro*. Preclinical *in vivo* models using SCY-078 for treatment of disseminated candidiasis have demonstrated promising potency and PK (142).

**New technologies for the assessment of CNS PK of antifungals**

Historically, studies assessing the CNS PK of antifungals *in vivo* have taken brain tissue homogenates and measured drug using LC-MS, as demonstrated in this review. Modern techniques enable more refined CNS PK models including information about the spatial distribution of drug within tissues. We have seen that PK differences in various brain compartments can be assessed using microdialysis. This technique measures drug penetration into fluid compartments of the CNS using a dialysis probe to detect free drug in the cerebral interstitial fluid. The use of microdialysis in humans is limited to intraoperative settings and the technique may be unsuitable for the quantification of highly protein-bound or lipophilic drugs (146). PET scanning and MR spectroscopy are non-invasive techniques that can estimate drug distribution into the human brain by detecting radiolabelled molecules. PET can provide longitudinal trends in drug distribution but its use is limited by cost, the inability to distinguish parent compounds from metabolites, and the requirement for radioactive labelling (17, 147, 148).

Matrix-Assisted Laser Desorption and Ionisation - Mass Spectroscopy Imaging (MALDI-MSI) does not require radiolabelling and can provide rapid, highly resolved spatial drug distribution data. In murine brains, MALDI-MSI has been employed to quantify a number of antibiotics including gatifloxacin (149), doxycycline (150), pretomanid (151) and rifampicin (152) to the subcompartmental level. Serial tissue sections taken over time can yield longitudinal data. The technique has not yet been applied to assess the CNS distribution of antifungal drugs. To do so could elucidate information regarding mechanisms of drug action, distribution and inter-subject variability in CNS drug penetration. This would enable precision spatial PK modelling with vastly enhanced translational utility from laboratory animals to humans and from plasma drug levels to those in the CNS.

**Declaration of interests**

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**Box 1: Desirable information for the accurate setting of PK-PD targets for fungal CNS infection**

1. Principal PK parameter of interest, depending on whether drug activity is determined by maximum concentration (Cmax), area under the curve (AUC), or time above a given therapeutic threshold.
2. Drug susceptibility/ minimum inhibitory concentration (MIC) of the infecting fungus.
3. Magnitude of the PK-PD index required, in terms of the unbound concentration of drug that is sufficient to exert PD effect on the target organism.
4. Histopathological site(s) of disease within the CNS.
5. Rate constant describing the movement of drug into the CNS from the circulation.
6. Rate constant(s) describing the movement of drug within CNS compartments of interest.
7. Rate constant(s) describing the clearance of drug from the target site.
8. Rate constant(s) describing the clearance of drug from the body.
9. Time-dependent differences in plasma and tissue drug concentrations (hysteresis).
10. PK parameters associated with toxicity in measurable physiological compartments (usually the systemic circulation).
11. Clinical and physiological covariates that influence the PK of the drug in question.
12. Population-level variability in each of these factors.

**Table 1**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Fungal species** | **Clinical setting** | **Predilection for CNS involvement in invasive disease** a § | **Pathophysiological manifestations** | **Mortality with treatment (%)** | **Antifungal drug options** | **References** |
| *Cryptococcus* spp.  *C. neoformans* | Advanced HIV infection, defective cellular immunity, corticosteroid therapy | ++++ | Subacute – chronic meningitis  Cerebral abscesses/ cryptococcomas  Cerebral infarction  Raised intracranial pressure | 24 – 58 | Amphotericin B  Flucytosine  High-dose fluconazole | (32, 33, 93, 153-158) |
| *C. gattii* | Normal hosts mainly in restricted geographical locations (Australia, Southern California, British Columbia, Washington State), solid organ transplant recipients | ++++ | Meningitis  Cryptococcomas  Raised intracranial pressure | 0 – 13 | (159-161) |
| *Coccidioides*  *C. immitis*  *C*. *posadasii* | HIV infection, steroid therapy, travel to southwest USA, Central and South America | +++ | Subacute – chronic meningitis (?basilar)  Cerebral abscesses  Cerebral vasculitis  Encephalitis | ~30 | Fluconazole  Itraconazole  Voriconazole  Intrathecal amphotericin B | (37, 162-166) |
| *Cladosporium* spp. | Immunodeficiency, immunosuppression, normal host, trauma | +++ | Intracerebral abscesses  Meningitis  Encephalitis | 29-50 | Amphotericin B in combination with vori-, itra- or posaconazole | (167-170) |
| *Aspergillus* spp. | Neutropenia, advanced HIV infection, haematopoetic stem-cell transplantation, corticosteroid therapy, chronic granulomatous disease | ++ | Cerebrovascular aspergillosis with cortical and subcortical infarction and haemorrhage  Abscesses  Rarely: chronic meningitis | 62 – 90 | Voriconazole  Amphotericin B  Isavuconazole  Consider: High dose adjunctive echinocandins | (171-174) |
| *Scedosporium/ Pseudallescheria* spp. | Neutropenia  Near-drowning | ++ | Chronic meningitis  Cerebral abscess | 79 – 100\* | *S. apiospermum*: voriconazole monotherapy  *S. prolificans:* voriconazole + terbinafine +/- echinocandin | (175-179) |
| *Candida* spp. | Prematurity, immunosuppression for haematological malignancies/ transplantation, invasive devices, burns, chronic granulomatous disease, advanced HIV infection | + | Subacute meningitis  Multiple micro-abscesses  Macroabscesses | 10 – 53 | Amphotericin B  Flucytosine  Fluconazole  Voriconazole in fluconazole-resistant disease | (180-184) |
| *Histoplasma capsulatum* | Advanced HIV infection  Primary or iatrogenic immunosuppression  Steroid therapy  Solid organ transplant recipients | + | Meningitis  Cerebral mass lesions  Diffuse encephalitis  Raised intracranial pressure  Cerebral vasculitis | 20 – 40 | Amphotericin B  Itraconazole  Fluconazole  Salvage therapy (limited data):  Posaconazole  Isavuconazole  Voriconazole | (81, 185-190) |
| *Blastomycosis dermatitidis* | Normal host mainly in restricted geographical locations (southeastern, south central and midwestern USA, St Lawrence river) | + | Chronic meningitis  Cerebral abscesses/ blastomycomas | ~18 | Amphotericin B  Step down to azole:  Voriconazole  Fluconazole  Itraconazole | (94, 175, 191, 192) |
| Mucormycosis/ Zygomycetes | Diabetes mellitus  Haematological malignancy | + | Rhino-orbital-cerebral infection  Cerebral abscesses | 25 – 62 | Amphotericin B  Step down to azole:  Posaconazole  Isavuconazole | (95, 193, 194) |
| *Sporothrix schenckii* | HIV infection  Alcoholism  Environmental exposure | + | Chronic meningitis  Encephalitis  Hydrocephalus | 30-90 | Amphotericin B  Step down:  Itraconazole | (96, 175) |
| *Paracoccidioides* *brasiliensis* | Environmental exposure, Latin America  Male predominance (~23:1) | +/- | Intracerebral abscesses  Spinal cord involvement  Hydrocephalus | ~17 | Trimethoprim-sulfamethoxazole  Voriconazole  Itraconazole | (175, 195-197) |
| *Trichosporon* spp. | Haematological malignancy, HIV infection, extensive burns, intravenous catheters, heart valve surgery | No data | Intracerebral abscesses  Meningitis | 70-80 | Amphotericin B  Voriconazole  Itraconazole  Posaconazole  Isavuconazole | (198, 199) |

\* Disseminated infection

a From (200)

§ Key: ++++, very common, through +/-, very rare

**Table 2**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Drug | Molecular weight (g/mol)a | Particle size (µm)b | LogP a | LogD at pH 7.4 (indicative of lipophilicity)b | Plasma protein binding (%)c | Efflux pump affinity (P-gp substrate) | Correlation of measurable CNS concentration with biological activity | References |
| Fluconazole | 309 |  | 2.17 | 0.5 | 10 | No | Good | (201-203) |
| Itraconazole | 705 |  | 6.99 | 4.9 | 98 | Yes | Poor | (202, 203) |
| Voriconazole | 349 |  | 2.56 | 2.1 | 58 | No | Good/ variable | (203) |
| Posaconazole | 700 |  | 6.1 | 4.4 | 99 | Yes | Poor | (203) |
| Isavuconazole | 718 |  | -3.33 | 3.6 | 99 | No | Good | (204, 205) |
| DAmB | 924 | <0.4 | 0.95 | -2.8 | >95 | No | Poor | (206, 207) |
| LAmB | 924 | 0.05 - 0.08 | 0.95 | -2.8 | >95 | Contentious | Poor | (14, 15, 207) |
| ABLC | 924 | 1.6 – 11 | 0.95 | -2.8 | >95 | No | Poor | (3, 207) |
| ABCD | 924 | 0.12 – 0.14 | 0.95 | -2.8 | >95 | No | Poor | (3, 207) |
| 5FC | 120 |  | -0.89 | -2.34 | 5 | No | Good | (3, 202) |
| Caspofungin | 1093 |  | -2.8 | -3.88 | 98 | No | Good | (208, 209) |
| Micafungin | 1140 |  | -3.8 | -1.62 | 98 | No | Good | (208, 209) |
| Anidulafungin | 1291 |  | 0.21 | -3.32 | 98 | No | Good | (116, 209) |

a From reference (3)

b From reference (2, 210)

c From references (3, 203)

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