Chapter 11
Personalized Management of Neurological Disorders

Introduction

Personalized neurology requires the integration of several neuroscientific and clinical aspects of neuropharmacology (Jain 2005c). Drug discovery for neurological disorders should take into consideration targeting a specific type in the broad clinical category of a neurological disease in the conventional clinical diagnosis. Drug delivery to the central nervous system (CNS) is an important factor in personalizing treatment of neurological disorders. Personalized management of some important neurological disorders such as Alzheimer's disease (AD), Parkinson's disease (PD), epilepsy, migraine, and multiple sclerosis (MS) will be considered in this chapter.

Personalized Drug Development for Neurological Disorders

Personalized Drug Discovery

CNS drug candidates fail approval in over 90% of the cases owing to problems in the delivery to the site of action in the brain, lack of efficacy, and unacceptable side effects. New drugs are badly needed for CNS disorders. The greatest activity is in the use of biomarkers as potential drug targets, but those for disease mechanism, efficacy, and toxicological effects are under investigation. Many of the biomarkers can later be developed as new diagnostic agents to guide personalized molecular therapy (Frost 2008).

Molecular Imaging and CNS Drug Development

In vivo imaging offers a pathway to reduce the risk of failure of drug molecules at each stage of development, but more research and development is needed to fully

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realize this potential. However, there are several examples of the usefulness of molecular imaging in CNS drug development. Use of PET in drug development can unravel the disease mechanism, measure the disease progression, demonstrate drug action in vivo, and enable the defining of drug-response curves for phase I and phase II studies. This can speed up drug development. The imaging agent PK11195 (GE Healthcare Bioscience) binds to peripheral benzodiazepine sites at microglia (20% of all non-neuronal cells in the brain) that are activated by injury or disease. Some applications of this technique as well as other imaging techniques in various CNS diseases are given below.

Multiple sclerosis (MS). ^{11}C-PK11195 can pick up inflammatory changes in both optic nerves in MS patients, which do not show up on ordinary MRI. It fulfils the need for a marker as a guide to interferon therapy for these patients.

Parkinson's disease (PD). ^{11}C-PK11195 PET can be used to follow the progression of inflammation in PD and its response to various therapies. ^{18}F-dopa PET can follow the progression of the disease from detection of dopamine deficit in an asymptomatic PD twin to clinical manifestations 5 years later. This method can also be used to test the effect of neuroprotective drugs in PD. Infusion of glial cell-derived neurotrophic factor (GDNF) into the putamen of PD patients demonstrates significant increases in ^{18}F-dopa uptake following 2 years of GDNF infusion.

Alzheimer's disease (AD). ^{11}C-PK11195 binding correlates with atrophy of left temporal lobe shown on MRI in AD patients and the course can be followed over a long period. It provides a chance to test various drugs and determine their action, e.g., if they have any neuroprotective effect. ^{18}F-FDDNP, a hydrophobic radiofluorinated derivative of 2-(1-[6-(dimethylamino)-2-naphthyl]ethylidene)malononitrile (DDNP), binds to synthetic beta-amyloid(1–40) fibrils, neurofibrillary tangles (NFTs), and amyloid plaques in human AD brain specimens.

^{18}F-FDDNP, in conjunction with PET, can be used to determine the localization and load of NFTs and beta-amyloid senile plaques in the brains of living AD patients. Greater accumulation and slower clearance is observed in amyloid plaque- and NFT-dense brain areas and correlated with lower memory performance scores. The relative residence time of the probe in brain regions affected by AD is significantly greater in patients with AD than in control subjects. This noninvasive technique for monitoring AP and NFT development is expected to facilitate diagnostic assessment of patients with AD and assist in response-monitoring during experimental treatments.

There is loss of glucose metabolism in AD usually measured by FDG-PET. This can also be measured by ^{11}C-PIB and the slope values correlate with the findings of FDG dementia index. ^{123}I-QNB SPECT can demonstrate M1 muscarinic receptor binding in AD. There is increased M1 binding in donepezil responders as compared to non-responders.

Personalized Management of AD

AD is a progressive degenerative disorder of the brain that begins with memory impairment and eventually progresses to dementia, physical impairment, and death. The cause of AD is not well understood but it likely comprises several processes that lead to intrinsic neuronal cell killing. Patients develop various psychiatric and neurological signs during the course of the disease. The prevalence rates of dementia vary significantly in different countries, but range from 2.1% to 10.5%. AD is the most common type of dementia, accounting for 50–60% of all cases. Pharmacogenomic aspects were described briefly in Chapter 4.

The diagnosis of AD is currently based on clinical and neuropsychological examination. There is currently no biomarker of AD for early detection. MRI and computer tomography (CT) scan images of hippocampus shrinkage and, later on, global brain shrinkage are used to help diagnose advanced disease. To date there is no definitive blood test available that can discriminate dementia patients from healthy individuals. A combination of characteristic plaque markers tau and amyloid β (Aβ) may constitute a specific and sensitive cerebrospinal fluid marker for AD. Genetic tests exist to identify individuals with familial forms of AD who have AD-linked mutations in the presenilin gene, and those who have specific variations in the ApoE gene linked to higher risk of developing AD. The ApoE e4 allele, a risk factor rather than a disease gene, has a positive predictive value of 94–98% in an individual with suspicion of AD. It is useful for predicting the response to certain drugs for AD.

A complex disease like AD is difficult to attack because no single approach is adequate and the development of a single universal therapy is unlikely. The mainstay of management of AD currently consists of cholinesterase inhibitors: rivastigmine, donepezil, and galantamine (Jain 2009o). Numerous neuroprotective therapies are under investigation but the only one currently marketed is memantine – a non-competitive *N*-methyl-D-aspartate antagonist. Proteolytic processing of the amyloid precursor protein (APP) generates Aβ peptide, which is thought to be causal for the pathology and subsequent cognitive decline in AD. The reduction in the levels of the potentially toxic Aβ peptide has emerged as one of the most important therapeutic goals in AD. Key targets for this goal are factors that affect the expression and processing of the βAPP.

Functional genomics, proteomics, pharmacogenomics, high-throughput methods, combinatorial chemistry, and modern bioinformatics will greatly contribute to accelerate drug development for AD. Genotype-specific responses of AD patients to a particular drug or combination of drugs have been demonstrated although several studies examining the role of ApoE produced conflicting results. A multifactorial therapy combining three different drugs yielded positive results during the 6–12 months in approximately 60% of the patients (Cacabelos 2002). With this therapeutic strategy, APOE-4/4 carriers were the worst responders, and patients with the APOE-3/4 genotype were the best responders. A study of the effect of galantamine

on cognitive performances in AD patients correlated it with apoE genotyping (Babic et al. 2004). A significant number of responders (71%) were observed among apoE4 homozygous patients. The subgroup of apoE4 homozygous patients with AD in its mild to moderate stage may be considered as responders to galantamine. The pharmacogenomics of AD may contribute in the future to optimize drug development and therapeutics, increasing efficacy and safety, and reducing side effects in accordance with the concept of personalized medicine.

Various isoforms of the nitric oxide (NO) producing NO synthase (NOS) are elevated in AD indicating a critical role for NO in the pathomechanism. The potential structural links between the increased synthesis of NO and the deposition of nitrotyrosine in AD, the expression of neuronal NOS (nNOS), induced NOS (iNOS), and endothelial NOS (eNOS) has been investigated in AD. Aberrant expression of nNOS in cortical pyramidal cells is highly co-localized with nitrotyrosine. Furthermore, iNOS and eNOS are highly expressed in astrocytes in AD. In addition, double immunolabeling studies reveal that in these glial cells iNOS and eNOS are co-localized with nitrotyrosine. Therefore, it is possible that increased expression of all NOS isoforms in astrocytes and neurons contributes to the synthesis of peroxynitrite, which leads to generation of nitrotyrosine. In view of the wide range of isoform-specific NOS inhibitors, the determination of the most responsible isoform of NOS for the formation of peroxynitrite in AD could be of therapeutic importance in the personalized treatment of AD.

Metabolomics of AD, which amplifies changes both in the proteome and the genome, can be used to understand disease mechanisms from a systems biology perspective as a noninvasive approach to diagnose and grade AD. This could allow the assessment of new therapies during clinical trials, the identification of patients at risk to develop adverse effects during treatment, and finally the implementation of new tools towards a more personalized management of AD (Barba et al. 2008).

Personalized Management of PD

PD is characterized by progressive degradation of dopaminergic (DA) neurons, which results in both cognitive as well as movement disorders. The drug most commonly prescribed for PD, levodopa is a precursor of dopamine. With the use of levodopa, a physician titrates dopamine up to an optimal level for movement and some aspects of cognition. However, the part of the nervous system, which is relatively normal, is overdosed making the drug perform aberrantly. That is why some patients react psychotically to levodopa. Knowing the neural bases of these differential effects will enable clinicians to modify the drug dose, or combine levodopa with other drugs, to produce the best outcome for individual patients and avoid such reactions. There is a trend now towards incorporating genetics into clinical studies of therapy for PD to investigate how a person's genetic make-up influences the effect of drugs that work by neurochemical intervention.

Cytochrome P450 CYP2D6 enzyme, which metabolizes many drugs, is also involved in the metabolism of dopamine. Prevalence of CYP2D6 4 allele differs significantly between the PD patients and normal subjects.

Entacapone, a drug used for the treatment of PD, inhibits catechol-*O*-methyltransferase (COMT) in a dose-dependent, reversible, and tight-binding manner but does not affect other catechol metabolizing enzymes. It enables the reduction of the levodopa dose. However, COMT genotype seems to be a minor factor in judging the beneficial effects of entacapone administration.

If gene polymorphisms that affect the metabolism of antiparkinsonian drugs can be identified, it might assist physicians in prescribing the drug dose that will balance short-term control of tremors with long-term drug side effects that eventually render PD untreatable.

Discovery of Subgroup-Selective Drug Targets in PD

Studies using global gene-expression profiles define the four major classes of DA and noradrenergic neurons in the brain. The molecular profiles obtained provide a basis for understanding the common and population-specific properties of catecholaminergic (CA) neurons and will facilitate the development of selective drugs. One of their goals is to identify genes that may influence the selective vulnerability of CA neurons in PD. The substantia nigra (SN) is most susceptible to PD pathology, whereas the adjacent ventral tegmental area (VTA) DA neurons are less vulnerable and hypothalamic DA neurons are spared. The sparing of VTA neurons could be mediated by selective expression of neuroprotective factors, including neurotrophic factors, detoxifying enzymes, lipoprotein lipase, etc. They also observed selective high expression of γ-synuclein in the neurons of the SN and in the locus coeruleus noradrenergic neurons that degenerate in PD, which may modify the toxic effects of the widely expressed α-synuclein protein. Likewise, selective expression of the Zn^{2+} transporter by the SN and VTA may play a role in the pathophysiology of PD. Low concentrations of Zn^{2+} can exert a cell-protective effect; however, excess of Zn 2^{2+} is neurotoxic and has been shown to promote degeneration of midbrain DA neurons. Thus the molecular signatures of the major classes of CA neurons improve our understanding of the characteristic features and functions of these neurons and facilitate the discovery of subgroup-selective drug targets.

Personalized Management of Epilepsy

Epilepsy is characterized by excessive neuronal activity (seizures) in the brain, typically causing muscle spasms, convulsions, and altered behavior. It is one of the most common neurological disorders and afflicts approximately 1–1.5% of the

population, i.e., approximately 50 million people affected world-wide. At least 2.5 million people in the US suffer from epileptic seizure disorders and 125,000 new cases are diagnosed every year. At least 20 different types of epilepsy have been identified. These patients can usually be divided into two major types: partial seizures (seizures that begin in a localized area of the brain)/epilepsy and generalized seizures/epilepsy. The mainstay of treatment is pharmacotherapy and the primary criterion for the selection of AED is the patient's seizure type.

Choice of the Right AED

Current treatment of epilepsy is imprecise. The mainstay of treatment for epilepsy is pharmacotherapy and the primary criterion for the selection of antiepileptic drugs (AEDs) is the patient's seizure type. This practice derives largely from drug studies that assess AED effectiveness for specific seizure types rather than the defined causes of seizures. Despite restriction to partial seizures, the response to an investigational AED is quite variable. The reasons for this include: (i) patient-to-patient variation in the metabolism of the AED; (ii) variations in the ability of AED to bind to the target; (iii) variations in the amount of AED target produced by different individuals; and (iv) different pathophysiological events accounting for the same seizure phenotype.

There are several old AEDs and several new drugs have been introduced in the past few years. However, no single AED is clearly superior to others. Causes of variability of effects of AEDs include genetic differences, pathogenesis and severity of epilepsy, age, nutritional status, renal and liver function, concomitant illnesses, and drug interactions. Physicians try to match a drug to the patient by trial and error. The final choice may take several months and depends on the efficacy and tolerability of adverse effects. However, the problems still remain of adverse side effects and failure to control seizures in more than 30% of patients.

Pharmacogenetics of Epilepsy

Pharmacogenetic alterations can affect efficacy, tolerability, and safety of AEDs, including variation in genes encoding drug target (SCN1A), drug transport (ABCB1), drug metabolizing (CYP2C9, CYP2C19), and human leukocyte antigen (HLA) proteins. The current studies associating particular genes and their variants with seizure control or adverse events have inherent weaknesses and have not provided unifying conclusions. However, several observations, for example, that Asian patients with a particular HLA allele, HLA-B*1502, are at a higher risk for Stevens-Johnson syndrome when using carbamazepine, are helpful in improving our knowledge of how genetic variation affects the treatment of epilepsy (Löscher et al. 2009). A better understanding of the genetic influences on outcome of

epilepsy is a key to developing the much needed new therapeutic strategies for individual patients with epilepsy.

Pharmacogenomics of Epilepsy

One of the difficulties in managing epilepsy is that the cause is unknown with the exception of seizures because of known pathology such as brain tumors and head injury. Epilepsy is mostly a multifactorial disorder although familial forms occur and some epilepsy genes have been identified. Currently there are no genetic tests for epilepsy. SNP association analysis shows that malic enzyme 2 (ME2) gene predisposes to idiopathic generalized epilepsy (Greenberg et al. 2005). ME2 is a genome-coded mitochondrial enzyme that converts malate to pyruvate and is involved in neuronal synthesis of the neurotransmitter gamma-aminobutyric acid (GABA). Disruption of the synthesis of GABA predisposes to seizures, which are triggered when mutations at other genes are present. It is also becoming increasingly clear that genetic polymorphisms play an integral role in variability in both AED pharmacokinetics and pharmacodynamics. Gene expression patterns of children on valproic acid monotherapy differ according to whether they have continuing seizures or remain free from seizures. This information can be used for personalizing antiepileptic therapy (Tang et al. 2004). The publication of the human genome and increasing sophisticated and powerful genetic tools offers new methods for screening drugs and predicting serious idiosyncratic side effects.

Control of epilepsy with phenytoin can be a difficult and lengthy process because of the wide range of doses required by different patients and the drug's narrow therapeutic index. Similarly, appropriate doses of carbamazepine take time to determine because of the drug's variable affects on patient metabolism and its potential neurologic side effects. People with epilepsy are genetically different from one another, and some of those differences affect their responses to drugs in a predictable manner. Variants of two genes have been identified that are more likely to be found in patients who require higher dosages of AEDs carbamazepine and phenytoin (Tate et al. 2005). One variant of the gene which encodes CYP2C9 shows a significant association with the maximum dose of phenytoin taken by patients with epilepsy. Moreover, a variant of a second gene, called SCN1A, with activity in the brain, is found significantly more often in patients on the highest doses of both carbamazepine and phenytoin. SCN1A has been implicated in many inherited forms of epilepsy and is the drug target for phenytoin. Detection of these gene variants might determine, in advance, which patients will need the higher dose and enable a more optimal dose schedule at the start. Otherwise it could take months to get the seizures under control. These new findings provide a direction for a dosing scheme that could be tested in a clinical trial to assess whether pharmacogenetic testing can improve dosing decisions. Such a trial might also enable physicians to identify patients who might safely take a smaller dose, thereby minimizing their risk for adverse side effects.

Drug Resistance in Epilepsy

Another problem with current therapy is development of drug resistance. One-third of patients with epilepsy develop resistance to drugs, which is associated with an increased risk of death and debilitating psychosocial consequences. Because this form is resistant to multiple AEDs, the mode of resistance must be nonspecific, involving drug-efflux transporters such as ATP-binding cassette sub-family B member 1 (ABCB1, also known as MDR1 and P-glycoprotein 170). A genotyping study has shown that patients with drug-responsive epilepsy, as compared to patients with drug-resistant epilepsy, were more likely (28% vs. 16%) to have the CC genotype at ABCB1 3435 than the TT genotype (Siddiqui et al. 2003). The polymorphism fell within an extensive block of linkage disequilibrium spanning much of the gene, implying that the polymorphism may not itself be causal but rather may be linked with the causal variant. The results of this study indicate that a genetic factor is associated with resistance to AEDs and suggest new avenues for early molecular prediction of drug resistance. Since 2003, several other association genetics studies have sought to confirm this result, but did not support a major role for this polymorphism. Lessons learnt from the ABCB1 studies can help guide future association genetics studies for multidrug resistance in epilepsy (Tate and Sisodiya 2007). Use of AEDs that are not ABCB1 substrates, inhibition of ABCB1 or the development of drugs that can evade ABCB1 might improve the efficacy of treatment in some patients with drug-resistant epilepsy. Further studies in this direction might eventually enable the drugs to be tailored to the patient's profile.

Cellular mechanisms underlying drug resistance have been studied by comparing resected hippocampal tissue from two groups of patients with temporal lobe epilepsy (TLE); the first displaying a clinical response to the anticonvulsant carbamazepine and a second group with therapy-resistant seizures (Remy et al. 2003). It was shown that the mechanism of action of carbamazepine, use-dependent block of voltage-dependent Na^+ channels, is completely lost in carbamazepine-resistant patients. Likewise, seizure activity elicited in human hippocampal slices is insensitive to carbamazepine. In marked contrast, carbamazepine induced use-dependent block of Na^+ channels and blocked seizure activity in vitro in patients clinically responsive to this drug. These data suggest that the study of changes in ion channel pharmacology and their contribution to the loss of anticonvulsant drug efficacy in human epilepsy may provide an important impetus for the development of novel anticonvulsants specifically targeted to modified ion channels in the epileptic brain. It is possible to use human tissue for the demonstration of drug resistance in an in vitro preparation, providing a unique tool in the search for novel, more efficient anticonvulsants.

A study of the properties of transmitter receptors of tissues removed during surgical treatment of drug-resistant TLE show use-dependent rundown of neocortical $GABA_A$-receptor (Ragozzino et al. 2005). This represents a TLE-specific dysfunction in contrast to stable $GABA_A$-receptor function in the cell membranes isolated from the temporal lobe of TLE patients afflicted with neoplastic, traumatic,

or ischemic temporal lesions and can be antagonized by BDNF. These findings may help to develop new treatments for drug-resistant TLE.

Another mechanism underlying drug resistance in epilepsy may be the same as in cancer: a cellular pump called P-glycoprotein, which protects cells from toxic substances by actively exporting the offending compounds. In one case that became resistant to phenytoin, low levels of phenytoin were demonstrated in association with high levels of P-glycoprotein expression, the product of the MDR1 gene. Currently, there are plenty of opportunities to develop personalized antiepileptic medicines because of the wide variations in effectiveness and adverse effect profile of current AEDs.

Future Prospects for Epilepsy

For the future, it is expected that several gene mutations will be identified in epilepsy using DNA biochips, e.g., those in ion channel genes. Future drugs may be designed specifically according to the electrophysiological dysfunction as personalized medicines for epilepsy. There is ample scope for penetration by new products with a benign side effect profile and/or higher effectiveness. Several new drugs are in development but there is still need for better drugs and strategies to overcome drug resistance.

Study of multidrug transporters is a fruitful area of epilepsy research. The knowledge that multidrug transporters are increased in epileptogenic areas opens new potential avenues for therapeutic intervention. Drugs can be developed to inhibit or bypass overexpressed transporters or implantable devices can be used to deliver high concentrations of drugs directly into the epileptogenic brain parenchyma.

Initial studies have focused on genes whose products play a putatively important role in AED pharmacology, particularly drug transporter proteins, drug metabolizing enzymes, and ion channel subunits. However, there is a lack of good correspondence between results from different laboratories, and more recent findings are awaiting attempts at confirmation. Thus, there are currently no AED treatment guidelines that are based on pharmacogenetic data. In order to begin to have clinical impact, the following recommendations have been made (Ferraro et al. 2006):

- Standards specific to the conduct of future AED studies must be established, particularly accurate epilepsy classification, appropriate AED selection, and clear and objective assessment outcome measures.
- General standards for analysis and interpretation of genetic association data must be better codified and applied consistently across studies.
- Extensive clinical research networks must be formulated and large numbers of well characterized patients must be recruited.

- Further development of these critical factors will optimize chances for overcoming current challenges posed by AED pharmacogenetic research and ultimately allow the realization of improved, more rational therapeutic strategies.

Personalized Management of Migraine

Migraine is a paroxysmal neurological disorder affecting up to 12% of males and 24% of females in the general population. Improvements in prophylactic, treatment of migraine patients are desirable because the drugs currently available are not effective in all patients, allow recurrence of the headache in a high percentage of patients and sometimes have severe adverse side effects. With a large number of triptans now available, it may be possible to match individual patient needs with the specific characteristics of the individual triptans to optimize therapeutic benefit. Genetic profiling of predisposition to migraine should facilitate the development of more effective diagnostic and therapeutic applications. The development of International Hap Map project could provide a powerful tool for identification of the candidate genes in this complex disease and pharmacogenomics research could be the promise for individualized treatments and prevention of adverse drug response (Piane et al. 2007). Pharmacogenomics will most likely provide a stronger scientific basis for optimizing drug therapy on the basis of each patient's genetic constitution (Tfelt-Hansen and Brøsen 2008).

Personalized Treatment of MS

MS is considered to be an autoimmune disease associated with abnormalities in immune regulation. Although the etiology and pathogenesis of MS is still controversial, a consistent feature of the pathology of the disease is entry of T cells into the CNS, which induces an autoimmune inflammatory reaction and initiates demyelination. Immunomodulating agents have markedly improved treatment of MS because they reduce the frequency and severity of relapses. Current therapies for MS include interferon-β (IFN-β), glatiramer acetate, natalizumab, and chemotherapy. These therapies decrease the number of relapses and partially prevent disability accumulation. However, their efficacy is only moderate, they have common adverse effects and impose a high cost on health systems. The wide heterogeneity of MS and the different biological responses to immunomodulatory drugs can be expected to contribute to differential treatment responses. Strategies that dissect the relationship between the treatment response and the biological characteristics in individual patients are valuable not only as a clinical tool, but also in leading to a better understanding of the disease. Examples of such approaches are:

1. In vitro and ex vivo RNA expression profiles of MS patients under treatment with IFN-β have been determined by cDNA microarrays. Non-responders and responders to IFN-β as assessed by longitudinal gadolinium-enhanced MRI scans and clinical disease activity differ in their ex vivo gene expression profiles. These findings will help to better elucidate the mechanism of action of IFN-β in relation to different disease patterns and eventually lead to optimized therapy.
2. An MS assay, gMS™ (Glycominds), enables staging of the predicted disease activity and identification of the most appropriate treatment strategy in patients presenting with a first demyelinating events.
3. T cell receptor (TCR)-based immunotherapy is feasible for MS patients if it is individualized according to TCR activation patterns of patients at different stages of the disease.
4. The current focus in the treatment of MS is on neuroprotection, i.e., therapy that stops or slows the progression of the disease in contrast to symptomatic treatment, which may not have any durable effect. Glatiramer acetate, approved for primary progressive form of MS, is a neuroprotective agent. A statistically significant association has been detected between glatiramer acetate response and a single nucleotide polymorphism in a TCR-β variant in patients with MS (Grossman et al. 2007).
5. MRI has become established as a reliable, sensitive, and reproducible technique for studying the pathophysiology of MS and provides a means for optimizing treatment for individual patients.
6. Early, active MS lesions show several immunopathological patterns of demyelination, which may explain differences in response to therapy in various patients. Therapeutic plasma exchange (TPE) has been successfully used to treat fulminant demyelinating attacks unresponsive to steroids. Patients with pattern II would be more likely to improve after TPE than those with other patterns since pattern II lesions are distinguished by prominent immunoglobulin deposition and complement activation (Keegan et al. 2005). This is the first evidence that differences in pathological subtypes of MS may predict response to treatment. Correlation of plasma exchange response to tissue pathology supports the hypothesis that different patterns of tissue damage in MS may require different treatment approaches. However, brain biopsies such as those undergone by the patients studied are not routinely done in MS patients. They are only performed for excluding other diagnoses such as tumor or infection. Therefore, it is necessary to identify specific biomarkers from blood, DNA or MRI, which can distinguish between these four patterns without the need for a brain biopsy.

MBP8298

MBP8298 (BioMS Medical) is a synthetic peptide that consists of 17 amino acids linked in a sequence identical to that of a portion of the human myelin basic protein (MBP). MBP8298 has been developed for the treatment of MS. The specificity of

the immune attack in MS at the molecular level is determined in each case by the HLA type of the individual patient, and HLA type is known to be one factor that contributes to susceptibility to MS. The MBP8298 synthetic peptide is a molecular replicate of the site of attack that is dominant in MS patients with HLA haplotypes DR-2 or DR-4. These HLA types are found in 65–75% of all MS patients.

The apparent mechanism of action of MBP8298 is the induction or restoration of immunological tolerance with respect to the ongoing immune attack at this molecular site. High doses of antigen delivered periodically by the intravenous route are expected to suppress immune responses to the administered substance. The potential benefit of MBP8298 for any individual patient is therefore expected to be related to the extent to which his or her disease process is dominated by the autoimmune attack at the site represented by this synthetic peptide. Results of a 24-month double-blind placebo-controlled clinical trial and 5 years of follow-up treatment showed that intravenous MBP8298 delayed disease progression in an HLA Class II-defined cohort of patients with progressive MS (Warren et al. 2006). A pivotal phase II/III clinical trial is in progress. MBP8298 can be considered as a personalized treatment of MS.

Pharmacogenomics of IFN-β Therapy in MS

Affymetrix 100 K SNP arrays have been used to identify 18 SNPs that may explain why some individuals respond better to IFN-β treatment for MS than others (Byun et al. 2008). The study was done on individuals with relapsing-remitting MS over 2 years. Then large-scale pharmacogenomic comparisons were done between those who responded positively to the treatment and those who did not. The researchers found that 18 of the 35 SNPs were significantly associated with positive interferon beta treatment response. Of these 18 mutations, 7 lie within genes and the remainder are in non-coding regions. Many of the detected differences between responders and nonresponders were genes associated with ion channels and signal transduction pathways. The study also suggests that genetic variants in heparan sulfate proteoglycan genes may be of clinical interest in MS as predictors of the response to therapy. Although additional research needs to be done to further validate the study and understand the functional role of interferon beta, the work has the potential to change the approach to MS treatment from a hit-and-miss one to a more systematic personalized management.

The BENEFIT (BEtaseron/Betaferon in Newly Emerging MS for Initial Treatment) study, incorporated pharmacogenetic and pharmacogenomic analyses to determine the genetic elements controlling MS. The data from this study suggest that early initiation of treatment with IFN-β1b prevents the development of confirmed disability, supporting its use after the first manifestation of relapsing-remitting MS (Kappos et al. 2007).

Expression levels of IFN response genes in the peripheral blood of MS patients prior to treatment could serve a role as biomarker for the differential clinical response to IFN-β (van Baarsen et al. 2008). Biomarkers of response to IFN-β

therapy in MS will enable responders and nonresponders to drugs to be identified, increase the efficacy and compliance, and improve the pharmaco-economic profile of these drugs. Systems biology can be used to integrate biological and clinical data for developing personalized treatment of MS (Martinez-Forero et al. 2008).

Understanding of the factors that underlie the therapeutic response is key to the identification of predictive biomarkers. Novel developments in pharmacogenomics research are helping to improve the understanding of the pharmacological effects of IFN therapy, and the identification of biomarkers that allow stratification of MS patients for their response to IFN-β. Ultimately, this information will lead to personalized therapy for MS (Vosslamber et al. 2009).

Future Prospects of Personalized Therapy of MS

In the near future, studies on susceptibility genes and pharmacogenetics will provide invaluable information concerning new drugs for the treatment of MS and better therapeutic regimens for these patients. Future approaches to MS should integrate clinical and imaging data with pharmacogenomic and pharmacogenetic databases to develop prognostic profiles of patients, which can be used to select therapy based on genetic biomarkers.

Personalized Management of Psychiatric Disorders

Psychopharmacogenetics

Variability of the drug response is a major problem in psychiatry. Between 30–50% of the patients do not respond adequately to initial therapy and it can take several months to find this out. A study of the pharmacogenomic and pharmacogenetic basis of these disorders is important.

Most psychiatric disorders, including schizophrenia, major depression, and bipolar disorder, are considered polygenic. Using SNPs or a small set of SNPs is considered to be an excellent tool to discover genes for psychiatric disorders and potentially an excellent tool for psychopharmacogenetics as well. There are, however, a few obstacles for their use: (1) high-throughput, low-cost genotyping assay systems; (2) definitions of good disease phenotype; (3) a good collaboration effort among geneticists, epidemiologists, and physicians; (4) good candidate gene(s). Selecting good candidate genes is particularly difficult at the current time, because pathophysiology is unknown in most psychiatric disorders. However, if one can identify a good candidate gene(s), an association study using SNPs has more statistical power than linkage analysis. It has been demonstrated that when dealing with a gene that contributes 1–5% additive effect to phenotype, a huge number of subjects (more than 3,000) is required for linkage study but not for association study.

Serotonin (5-hydroxytryptamine, 5-HT) appears to play a role in the pathophysiology of a range of neuropsychiatric disorders, and serotonergic agents are of central importance in neuropharmacology. Recently, pharmacogenetic research has begun to examine possible genetic influences on therapeutic response to drugs affecting the serotonin system. At the Department of Psychiatry of the University of Chicago (Chicago, IL), genes encoding various components of the 5-HT system are being studied as risk factors in depression, schizophrenia, obsessive-compulsive disorder, aggression, alcoholism, and autism. Genes regulating the synthesis (TPH), storage (VMAT2), membrane uptake (HTT), and metabolism (MAOA) of 5-HT, as well as a number of 5-HT receptors (HTR1A, HTR1B, HTR2A, HTR2C, and HTR5A), have been studied. The critical and manifold roles of the serotonin system, the great abundance of targets within the system, the wide range of serotonergic agents – available and in development – and the promising preliminary results suggest that the serotonin system offers a particularly rich area for pharmacogenetic research.

COMT Genotype and Response to Amphetamine

Monamines subserve many critical roles in the brain, and monoaminergic drugs such as amphetamine have a long history in the treatment of neuropsychiatric disorders and also as a substance of abuse. The clinical effects of amphetamine are quite variable, from positive effects on mood and cognition in some individuals, to negative responses in others, perhaps related to individual variations in monaminergic function and monoamine system genes. A functional polymorphism (val158-met) in the catechol *O*-methyltransferase (COMT) gene has been shown to modulate prefrontal dopamine in animals and prefrontal cortical function in humans. Amphetamine enhanced the efficiency of prefrontal cortex function assayed with functional MRI during a working memory task in subjects with the high enzyme activity valve genotype, who presumably have relatively less prefrontal synaptic dopamine, at all levels of task difficulty (Mattay et al. 2003). In contrast, in subjects with low activity met/met genotype who tend to have superior baseline prefrontal function, the drug had no effect on cortical efficiency at low-to-moderate working memory load and caused deterioration at high working memory load. These data illustrate an application of functional neuroimaging in pharmacogenomics and extend basic evidence of an inverted-U functional-response curve to increasing dopamine signaling in the prefrontal cortex. Further, individuals with the met/met COMT genotype appear to be at increased risk for an adverse response to amphetamine.

Genotype and Response to Methylphenidate in Children with ADHD

Attention deficit hyperactivity disorder (ADHD) is one of the most common neuropsychiatric disorders in children and adolescents. Many different medications

are available to treat ADHD, yet little data exists to guide treatment choices, which is often based on trial and error. Stimulant medications, such as methylphenidate are the most commonly used, effective treatment for ADHD. Methylphenidate acts primarily by inhibiting the dopamine transporter (DAT), a protein responsible for the reuptake of dopamine from the synapse into presynaptic terminals. However, it is often difficult to predict how patients will respond to ADHD medications.

A double-blinded, crossover trial found that children with a variant form of a DAT gene, 9/9-repeat DAT1 3′-UTR genotype, responded poorly to methylphenidate in contrast to those with 10/10-repeat variant who showed excellent response (Stein et al. 2005). This study shows that testable genetic differences might be used to predict the effectiveness of methylphenidate in children with ADHD. Further research is needed to determine the mechanisms related to poor response in patients with the 9/9-repeat genotype, and to determine if this group responds differentially to alternative treatments. A larger study is in progress to evaluate children with ADHD on two other medications to see if their genes predict who will respond to either or both drugs.

Personalized Antipsychotic Therapy

Although considerable advances have taken place in the pharmacotherapy of schizophrenia, 30–40% of schizophrenic patients do not respond to antipsychotic treatment and approximately 70% of them develop side effects. This variability in treatment response may have a genetic origin in two areas:

1. Genetic mutations in metabolic enzymes can render them inactive and result in the toxic accumulation of drugs or drug metabolites.
2. Genetic variation in drug-targeted neurotransmitter receptors can influence their binding and functional capabilities, affecting the efficacy of the treatment.

A combination of genetic information in drug dynamic and kinetic areas can be used to predict treatment response. Pretreatment prediction of clinical outcome will have a beneficial impact on psychiatric treatment. SureGene LLC is developing AssureGene test, a DNA-based diagnostic test for schizophrenia, to help personalize the treatment for this condition. Personalized antipsychotic treatment will improve recovery and diminish drug-induced side effects. Further investigations on gene expression and gene-environment interactions will improve the accuracy of the predictions.

It is possible to predict the clinical response to an antipsychotic drug such as clozapine. Several liver cytochromes such as CYP1A2 and CYP3A4 are involved in clozapine metabolism and interindividual variations in plasma levels of this drug are known. CYP1A2 knockout mice have a significant decrease in clozapine clearance compared with wild-type mice and the prolonged half-life of plasma clozapine suggests that CYP1A2 is involved in clozapine metabolism in an animal model.

Association studies in multiple candidate genes have been carried out to find polymorphisms that predict response to clozapine in schizophrenia patients. Based on clozapine binding profiles, several dopamine, serotonin, histamine, and adrenergic receptor polymorphisms have been studied. A combination of receptor polymorphisms can predict antipsychotic medication response. Clozapine has demonstrated superior efficacy, but because of potential serious side effects and necessary weekly blood monitoring, psychiatrists are sometimes hesitant to use it. However, as this study shows, if one is able to predict clozapine's response in advance, more patients will benefit from its use. This research method will also be applied to other antipsychotic medications. In future, simple psychopharmacogenetic tests will improve antipsychotic medication treatment and its application among individuals.

The ability of dopamine receptor polymorphism to predict clinical response to clozapine has been studied using PET. Studies with PET using FDG and dopamine D3 receptor polymorphism in the promoter region for genetic association have shown significant metabolic decrease in the frontal and temporal lobes, basal ganglia, and thalamus overall. The clinical responses can be correlated with genotypes. The approach of combining pharmacogenetics and imaging techniques offers the potential for understanding the clinical response to treatment and may predict side effects.

Many antipsychotics, including perphenazine, zuclopenthixol, thioridazine, haloperidol, and risperidone, are metabolized to a significant extent by the polymorphic cytochrome P450 (CYP) 2D6, which shows large interindividual variation in activity. Significant relationships between CYP2D6 genotype and steady-state concentrations have been reported for perphenazine, zuclopenthixol, risperidone, and haloperidol when used in monotherapy. Other CYPs, especially CYP1A2 and CYP3A4, also contribute to the interindividual variability in the kinetics of antipsychotics and the occurrence of drug interactions. For many antipsychotics, the role of the different CYPs at therapeutic drug concentrations remains to be clarified. Some studies have suggested that poor metabolizers for CYP2D6 would be more prone to oversedation and possibly parkinsonism during treatment with classical antipsychotics, whereas other, mostly retrospective, studies have been negative or inconclusive. For the newer antipsychotics, such data are lacking. Whether phenotyping or genotyping for CYP2D6 or other CYPs can be used to predict an optimal dose range has not been studied so far. Genotyping or phenotyping can today be recommended as a complement to plasma concentration determination when aberrant metabolic capacity (poor or ultrarapid) of CYP2D6 substrates is suspected. Enzymes that metabolize antipsychotics are shown in Table 11.1. Further prospective clinical studies in well-defined patient populations and with adequate evaluation of therapeutic and adverse effects are required to establish the potential of pharmacogenetic testing in clinical psychiatry.

ACADIA Pharmaceuticals is collaborating with the Karolinska Institute (Stockholm, Sweden) to examine possible genetic variations in schizophrenic patient populations that may contribute to differential responses to atypical and typical (i.e., clozapine and haloperidol, respectively) antipsychotic drugs. ACADIA's proprietary technology, a massively parallel, drug discovery engine, is called

Table 11.1 Enzymes that metabolize antipsychotics

Drug	CYP2D6	CYP2C19	CYP3A4	CYP1A2
Chlorpromazine	+			
Clozapine	+		+	+
Fluphenazine				+
Haloperidol	+		+	+
Olanzapine		+	+	
Perphenazine	+			
Risperidone	+			
Sertindol	+			+
Thiorodazine	+	+		
Zuclopentixol	+			

Receptor Selection and Amplification Technology (R-SAT). Once the contributing factors to genetic variation in drug response are determined from these and other studies, a pre-emptive strike can be initiated. Drug discovery programs can be redesigned to mitigate the impact of genetic variation in drug response or alternately clinical trials can be designed to treat only those patients exhibiting genetic variation that correlates with drug efficacy. Safer and more effective medicines should arise when this information is incorporated into the drug discovery process.

Nanogen acquired rights to genetic biomarkers related to schizophrenia and responses to antipsychotic therapies from the Co-operative Research Centre for Diagnostics and Queensland University of Technology in Australia. Nanogen plans to utilize the biomarkers to create diagnostic tests for schizophrenia and related conditions. Some of these biomarkers may also help predict adverse drug reactions (ADR) and therefore guide therapeutic decision-making.

ADRs to antipsychotic therapy constitute another area of concern. The CYP2D6 poor metabolizer phenotype appears to be associated with risperidone ADRs and discontinuation due to ADRs. This finding was revealed by genetic tests that were performed by allele-specific polymerase chain reaction and/or by the AmpliChip CYP450 microarray system for up to 34 separate CYP2D6 alleles (de Leon et al. 2005). Two logistic regression models with dependent variables (moderate-to-marked ADRs while taking risperidone and risperidone discontinuation due to ADRs) were evaluated with respect to the CYP2D6 phenotype.

Two genes are associated with tardive dyskinesia (a movement disorder) as an adverse reaction to antipsychotic treatment in psychiatric patients: one is dopamine D3 receptor, which involves pharmacodynamics of antipsychotics and the other is CYP1A2, which involves pharmacokinetics of antipsychotics. These two polymorphisms have an additive effect for tardive dyskinesia. These SNPs may be useful for predicting potential side effects from medications.

Resperidol's antipsychotic action is probably mainly explained by the blocking of dopamine receptors, particularly D2 receptors. There are polymorphic variations of this gene DRD2, but it is not clear that they have clinical relevance in predicting ADRs or antipsychotic response. Previous exposure to antipsychotics increases the

need for higher resperidol dosing, but the mechanism for this tolerance is not well understood. Other brain receptors, such as other dopamine, serotonin, and adrenergic receptors may explain some of these ADRs. Some polymorphic variations in these receptors have been described, but they cannot yet be used to personalize resperidol dosing (de Leon et al. 2008).

Personalized Antidepressant Therapy

After multiple trials, approximately 85% of patients respond to antidepressant treatment. However, only 60–65% respond to any one drug and response to treatment usually takes 4–8 weeks, if the drug works. A failed first treatment is the best predictor of treatment dropout and treatment dropout is the best predictor of suicide. Pharmacogenomic approaches could help in predicting some of these outcomes. Enzymes that metabolize antidepressants are shown in Table 11.2.

Although antidepressant response takes weeks, the effects of antidepressants on monoamine systems is very rapid. Therefore, it is possible that the therapeutic effects of all antidepressants are due to common expression of genes after chronic treatment. The first step toward answering this question is finding out which transcripts are increased or decreased by antidepressant treatment. Such research can be done using an animal model. If a particular system is found to be responsible for the therapeutic effects of antidepressants, a new antidepressant pharmacotherapy could be developed to activate that system more acutely. A 5-HT_6 receptor polymorphism (C267 T) is associated with treatment response to antidepressant treatment in major depressive disorder (Lee et al. 2005). A pharmacogenomic approach to individualize antidepressant drug treatment should be based on three levels:

1. Identifying and validating the candidate genes involved in drug-response
2. Providing therapeutic guidelines
3. Developing a pharmacogenetic test-system for bedside-genotyping

Table 11.2 Enzymes that metabolize antidepressants

Drug	CYP2D6	CYP2C19	CYP3A4	CYP1A2
Amitripyline	+	+	+	+
Nortriptyline	+			
Imipramine	+	+	+	+
Desipramine	+			
Clomipramine	+	+	+	+
Citalopram		+	+	
Fluoxetine	+			
Fluvoxamine	+			+
Moclobemid		+		
Paroxetine	+			
Sertraline			+	
Venlafaxine	+		+	

Although personalized medication that is based on pharmacogenomic/pharmacogenetic data is expected to improve the efficacy of treatments for depression, the complexity of the regulation of gene transcription and its interactions with environmental factors implies that straightforward translation of individual genetic information into tailored treatment is unlikely. However, integration of data from genomics, proteomics, metabolomics, neuroimaging, and neuroendocrinology could lead to the development of effective personalized antidepressant treatment that is based on both genotypes and biomarkers (Holsboer 2008).

Pretreatment EEG to Predict Adverse Effects to Antidepressants

Changes in brain activity prior to treatment with antidepressants can flag patient vulnerability. Quantitative electroencephalography cordance measures revealed that changes in brain function in the prefrontal region during the 1-week placebo lead-in were related to side effects in subjects who received an antidepressant (Hunter et al. 2005). This study is the first to link brain function and medication side effects and show a relationship between brain function changes during brief placebo treatment and later side effects during treatment with medication.

The findings show the promise of new ways for assessing susceptibility to antidepressant side effects. The ability to identify individuals who are at greatest risk of side effects would greatly improve the success rate of antidepressant treatment. For example, physicians might select a medication with a lower side-effect profile, start medication at a lower dose, or choose psychotherapy alone when treating patients susceptible to antidepressant side effects.

Individualization of SSRI Treatment

The introduction of the selective serotonin reuptake inhibitors (SSRIs) has significantly transformed the pharmacological treatment of several neuropsychiatric disorders, particularly of individuals affected by depression, panic disorder, obsessive-compulsive disorder, and social phobia. Compared with the previous generation of psychotropic drugs, SSRIs offer an improved tolerability to therapy while maintaining a high level of efficacy. Nevertheless, despite these advantages, not all patients benefit from treatment; as some do not respond adequately, while others may react adversely. This necessitates a review of the initial treatment choice, often involving extended periods of illness while a more suitable therapy is sought. Such a scenario could be avoided were it possible to determine the most suitable drug prior to treatment.

The influence of genetic factors on SSRI efficacy now represents a major focus of pharmacogenetics research. Current evidence emerging from the field suggests that gene variants within the serotonin transporter and cytochrome P450 drug-metabolizing enzymes are of particular importance. It also appears likely that further key participating genes remain to be identified. A study in progress at the

Pharmacogenetics Research Network at the University of California (UCLA, Los Angeles) is investigating the genetic basis of response to fluoxetine and desipramine among Mexican-Americans, in part by identifying novel SNPs that may be relevant to the differing response to antidepressants. The most important areas for future research are exploration of known candidate systems and the discovery of new targets for antidepressants, as well as prediction of clinical outcomes. By comprehensively delineating these genetic components, it is envisaged that this will eventually facilitate the development of highly sensitive protocols for individualizing SSRI treatment.

Genes may influence susceptibility to depression and response to drugs. Because every person has two versions of the serotonin transporter genes, one inherited from each parent, the brain may have only long transporters (ll), only short transporters (ss) or a mixture of the two (ls). Even having one copy of the s gene produces susceptibility to depression and reduced response to SSRIs. Chronic use of 3,4-methylenedioxymethamphetamine (MDMA, or Ecstasy), a serotonin transporter, is associated with higher depression scores owing to abnormal emotional processing in individuals with the ss and ls genotype but not those with the ll genotype (Roiser et al. 2005). These findings indicate that SSRIs probably will not be effective for Ecstasy-induced depression.

The Mayo Clinic (Rochester, MN) is offering a new genetic test through Mayo Medical Laboratories to help US physicians identify patients who are likely to have side effects from drugs commonly used to treat depression. Mayo has obtained a nonexclusive license from Pathway Diagnostics Inc to test for a key genetic biomarker, 5HTT-LPR, which identifies people who respond differently to antidepressants, including SSRI. SSRIs act specifically by binding to the serotonin transporter, and increase the concentration of the neurotransmitter serotonin in the synapse. These medications include fluoxetine, sertraline, paroxetine, citalopram, and escitalopram.

The 5HTT-LPR biomarker has potential to improve management of patients with major depression and others who benefit from SSRI treatment. It provides unique information relating to drug response, namely, side effect and compliance. The ll genotype confers compliance to a SSRI whereas the ss genotype indicates an increased compliance with a noradrenergic and specific serotonergic antidepressant (e.g., mirtazapine). The serotonin transporter genotype assists the physician in making a better choice of antidepressant medications for their patients based upon their serotonin transporter genotype used in conjunction with CYP450 genotyping. Depending upon genotypes, some patients should respond well to SSRIs, some may respond to SSRIs but more slowly, and some patients may respond more effectively to non-SSRI antidepressants.

International guidelines for rational therapeutic drug monitoring (TDM) are recognized for personalized treatment with antidepressants and antipsychotics. Retrospective analysis of genotyping of patients with depression suggests a good agreement between the poor metabolism (PM) and ultrarapid metabolism (UM) genotypes, the TDM data, and clinical outcome (Sjoqvist and Eliasson. 2007). TDM combined with genotyping of CYP2D6 is particularly useful in verifying concentration-dependent ADRs due to PM and diagnosing pharmacokinetic reasons,

e.g., UM for drug failure. This is because ADRs may mimic the psychiatric illness itself and therapeutic failure because of UM may be mistaken for poor compliance with the prescription.

Vilazodone with a Test for Personalized Treatment of Depression

Vilazodone (Clinical Data Inc.), a dual SSRI and a 5HT1A partial agonist, is in phase III development in parallel with genetic biomarkers to guide its use as an antidepressant. As approximately one-half of depressed patients do not achieve satisfactory results with current first-line treatment options, a product that combines a genetic test with vilazodone will assist physicians in matching patients with a drug that is more likely to be effective for each patient in the first instance. In 2007, the primary and supportive secondary efficacy endpoints were met in the randomized, double-blind, placebo-controlled trial. In addition, the study separately identified candidate biomarkers for a potential companion pharmacogenetic test for response to vilazodone.

Summary

Personalized neurology requires the integration of several neuroscientific and clinical aspects of neuropharmacology. Molecular imaging is important for CNS drug discovery and development. The pharmacogenomics of neurodegenerative disorders may contribute in the future to optimize drug development and therapeutics, increasing efficacy and safety, and reducing side effects in accordance with the concept of personalized medicine.

Despite numerous AEDs in the market, treatment of epilepsy is unsatisfactory. Gene mutations are being identified in epilepsy, e.g., those in ion channel genes. Future drugs may be designed specifically according to the electrophysiological dysfunction as personalized medicines for epilepsy. The wide heterogeneity of MS and the different biological responses to immunomodulatory drugs contribute to different treatment results. Considerable efforts are under way to personalize treatment of this disease. In the near future, studies on susceptibility genes and pharmacogenetics will provide invaluable information concerning new drugs for the treatment of MS and better therapeutic regimens for these patients. This chapter also considers the personlization of psychiatric treatment particularly that involving antipsychotics and antidepressants.