The importance of pharmacogenetics in the treatment of epilepsy

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Introduction

- Epileptic disorders are a group of chronic and sometimes progressive diseases, which involve approximately 1% of patients in all populations.
- Although there are more than 30 antiepileptic drugs, 30% of the patients, especially those with partial seizures originated from temporal or frontal lobe, are still resistant to pharmacotherapy.
- Furthermore, most of the antiepileptic drugs are reasonably toxic and have very narrow therapeutic window.

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Genetic variations

- There are important pharmacodynamic and pharmacokinetic variations for a particular antiepileptic drug among different patients because of genetic variations which include metabolization, and elimination pathways of antiepileptics.

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Overall examples

- Polymorphism in:
  Enzymes
  Ion channels
  Receptors
  Transporters

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Explanations for variations

- The first set of possible explanations for variations in efficacy and safety:
- The severity of the disease
- Organ dysfunctions such as liver and kidney
- Concomitant diseases, age, sex
- Feeding behaviors of the patients

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The genome

- However the "*genome*", the complete DNA sequence of the patients plays probably the most important role and it effects all of the other factors.
- Therefore epilepsy should be managed in a "*tailor-made*" manner in all patients.

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Tailor-made management of patients

- These approaches include:
- Advanced therapeutic drug monitoring
- Screening of cytochrome P450 enzymes

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Genetic explanation for epilepsy I

- Some of the so called idiopathic epileptic syndromes such as autosomal dominant nocturnal frontal lobe epilepsy, benign neonatal convulsions, generalized epilepsy with febrile seizures plus, childhood absence epilepsy with febrile seizures etc. now have genetic explanations.
- The others, which still remain idiopathic will probably be defined similarly soon.

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Genetic explanation for epilepsy II

Epileptic syndrome	Mutated channel
Benign neonatal convulsions (type 1 and 2)	Voltage gated K^+ channels KCNQ2 and KCNQ3
Autosomal dominant frontal lobe epilepsy	Nicotinic Ach receptor α_4- and β_2-subunits
Generalized epilepsy with febril seizures plus (GEFS+)	Voltage gated Na^+ channel β_1-, α_1- and α_2-subunits
Childhood absence epilepsy with febril seizures	$GABA_A$ channel α_2-subunit

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Development of antiepileptics

- Antiepileptic drugs have been traditionally screened in acute seizure models in normal adult rodents.
- The other and more sophisticated models such as kindling, auditory-induced seizures, chronic models of epilepsy, genetically modified animals are not commonly used in preclinical screening.

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Recently introduced antiepileptics

- The recently introduced antiepileptic drugs such as felbamate, gabapentin, tiagabine, topiramate, and zonisamide are not considerably more effective than the older ones but may result in less adverse events.

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The importance of pharmacogenetics

- Having more knowledge in pharmacogenetics, pharmacoresistant cases and side effects will be prerecognized.
- Moreover, the identification of a gene and gene product will allow a directed approach towards drug development.

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Drug metabolizing enzymes

Pharmacogenetics of drug metabolism

- In recent years genetic studies involving drug-metabolizing enzyme systems have greatly expanded our understanding of cytochrome enzymes and pharmacogenetics of drug metabolism.
- Among these progresses the most important features regarding drug interactions concern genetic polymorphisms and some other characteristics (inhibition and induction) of cytochrome enzymes.

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AEDs and their elimination I

- The most important phase I oxidizing enzyme systems that are responsible for the metabolism of many antiepileptic drugs concern CYP450 enzyme families.
- Phase II enzymes involving antiepileptic drugs metabolism include UDP–glucronosyl transferase (UGT).

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AEDs and their elimination II

Drug	Elimination
Carbamazepine	CYP3A4, CYP1A2, CYP2C8
Clobazam	CYP?
Clonazepam	CYP3A4, N-acetyltransferase
Ethosuximide	CYP3A4, CYP2E1, CYP2C9?, CYP2B?
Felbamate	CYP2E1, CYP3A4, (40–50% unchanged in urine)
Gabapentin	Renal unchanged
Lamotrigine	UGT1A3, UGT1A4
Levetiracetam	Renal unchanged, nonhepatic hydrolysis
Oxcarbazepine	Ketoreductase, UGT and limited CYP450

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AEDs and their elimination III

Drug	Elimination
Phenitoin	CYP2C9, CYP2C19, CYP2C8, CYP3A, and UGT
Phenobarbital	CYP2C9, CYP2E1,CYP2C19, UGT
Primidon	CYP2E1,CYP2C9?,CYP2C19?, and UGT
Tiagabine	CYP3A4
Topiramate	Renal unchanged and UGT,
Valproic acid	CYP2C9, CYP2C19, CYP2A6, CYP2B6, UGT1A9, UGT2B7, β-oxidation
Vigabatrin	Renal unchanged
Zonisamide	CYP3A4

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AEDs metabolized via CYP3A4

- Carbamazepine
- Clonazepam
- Ethosuximide
- Felbamate
- Phenitoin
- Tiagabine
- Zonisamide

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Genetic polimorphism of enzymes I

- Genetic polymorphism of drug-metabolizing enzymes is defined as ability of individuals to metabolize drugs in different degrees due to differences in the enzyme capacity and function.
- Concerning genetic polymorphism of a drug-metabolizing enzyme some phenotypes are considered poor metabolizers, because their drug metabolism is slower then the rest of a population.

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Genetic polimorphism of enzymes II

- Some individuals called ultraextensive metabolizers possess isoenzymes with the ability to metabolize drugs rapidly.
- There are also average metabolizers, called extensive metabolizers who may transform to poor metabolizers by enzyme inhibiting drugs.

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CYP450 polymorphism

- The polymorphism in CYP450 enzymes may be one of the reasons for the variability of antiepileptic drug interactions.
- This phenomenon is more important for drugs like phenytoin which has enzyme saturation kinetics and narrow therapeutic index.
- The subjects with polymorphism of CYP2C9 and 2C19 isoenzymes, which are responsible for the metabolism of phenytoin, are poor metabolizers and they are more vulnerable for drug interactions when an enzyme-inhibiting drug (e.g. fluvoxamine) is co-administrated with phenytoin.

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CYP2C9 genotypes in Turkey

CYP2C9	n (%)	n	p-HPPH / phenytoin
*1/*1	308 (61.7)	68	0.43
*1/*2	90 (18.2)	13	0.26
*2/*2	5 (1.0)	3	0.14
*1/*3	86 (17.2)	16	0.21
*2/*3	6 (1.1)	-	-
*3/*3	4 (0.8)	1	0.02
Total	499 (100.0)	101	

Aynacıoglu et al. Clin Pharmacol Ther 1999

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CYP2C19 genotypes

CYP2C19 genotypes	Turks n (%)	Germans n (%)	p
*1/*1	307 (76.0)	237 (72.3)	n.s.
*1/*2	90 (22.3)	76 (23.2)	n.s.
*1/*3	3 (0.7)	1 (0.3)	n.s.
*2/*2	4 (1.0)	14 (4.3)	0.007
Total	404 (100.0)	328 (100.0)	

Aynacıoglu et al. Clin Pharmacol Ther 1999

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CYP2C19 alleles

CYP2C19 alleles	Turks n (%)	Germans n (%)	p
wt (*1)	707 (87.5)	551 (84.0)	n.s.
m1 (*2)	98 (12.1)	104 (15.9)	0.047
m2 (*3)	3 (0.4)	1 (0.1)	n.s.
m3 (*4)	0 (0.0)	0 (0.0)	n.s.
m4 (*5)	0 (0.0)	0 (0.0)	n.s.
Total	404 (100.0)	328 (100.0)	

Aynacıoglu et al. Clin Pharmacol Ther 1999

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- There is also interindividual variability in inducibility.
- These variants may contribute to investigations of possible correlations between genotypes and disease-susceptibility phenotypes or responsiveness to drug therapy.

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AEDs and enyzme induction I

Drugs	Enzymes induced
Phenobarbital	CYP1A2, CYP2B, CYP2C8, CYP3A4, UGT
Phenitoin	CYP1A2, CYP2B, CYP3A4
Primidone	CYP1A2, CYP2B, CYP2C8, CYP3A4, UGT
Carbamazepine	CYP1A2, CP2C9, CYP3A4, CYP2C19?
Oxcarbazepine	CYP3A4 (weak)
Felbamate	CYP3A4
Lamotrigine	UGT (weak)

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AEDs and enyzme induction II

Drugs	Enzymes induced
Levetiracetam	Not affected
Valproic acid	Not affected
Vigabatrin	Not affected
Zonisamide	Not affected
Clonazepam	No data available
Gabapentin	No data available
Tiagabine	No data available
Topiramate	No data available

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Conclusion for enzymes

- Both phase I and II enzymes are involved in the metabolism of antiepileptic drugs, and their variability is of importance in the treatment of epilepsy.

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Presence of multiple drug resistance genes

ATP-binding cassette superfamily

- ATP-binding cassette (ABC) is a rapidly growing superfamily of integral proteins that has more than 250 members described so far, which in human also include several other multidrug resistance membrane proteins. MDR/TAP is one of its subfamilies.
- They become more important in experimental pharmacology and pharmacotherapy day by day especially in sense of genetics.

Source: http://www.gene.ucl.ac.uk/nomenclature/genefamily/abc.html

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MDR/TAP (subfamily B)

- MDR/TAP subfamily has 12 members described:
- ABCB1, TAP1, TAP2, ABCB4, ABCB5, ABCB6, ABCB7, ABCB8, ABCB9, ABCB10, ABCB10P, and ABCB11.

MDR: Multiple drug resistance gene

TAP: Transporter associated with antigen processing

Source: http://nutrigene.4t.com/humanabc.htm

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MDR1 and P-glycoprotein

- MDR1 is present in many tissues' apical membranes, especially those with barrier functions such as liver, blood brain barrier, kidney, intestine, and placenta.
- MDR1 is linked to ABCB1, it encodes P-glycoprotein, an energy-dependent efflux pump that exports planar hydrophobic molecules from the cell and it has broad substrate specificity.
- It is responsible for decreased drug accumulation in multidrug-resistant cells and often mediates the development of resistance to anticancer drugs.

Source: http://nutrigene.4t.com/humanabc.htm

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MDR1 and epilepsy

- P-glycoprotein is expressed in brain of some patients with intractable epilepsy and AEDs are exported by P-glycoprotein.
- Antiepileptic drugs are inadequately accumulated in brain of these patients.
- Lower intraparenchymal drug concentrations could contribute to lack of drug response in such patients.

Tishler DM et al Epilepsia. 1995; 36: 1-6

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CFTR/MRP (subfamily C)

- CFTR/MRP subfamily has 5 members described in human gene:
  ABCC1, ABCC2, ABCC3, ABCC4, ABCC5.
- It has 8 members described in mouse gene:
  ABCC6, CFTR, ABCC8, ABCC9, ABCC10, ABCC11, ABCC12, ABCC13.

CFTR: Cystic fibrosis transmembrane regulator
MRP: Multiple drug resistance-associated protein

Source: http://nutrigene.4t.com/humanabc.htm

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MRP1 gene

- MRP1 (ABCC1) is present in many tissues including lung, testes, PBMC in lateral membranes.
- MRP1 functions as a multispecific organic anion transporter, with (oxidized) glutathione, cysteinyl leukotrienes, and activated aflatoxin B1 as substrates. This protein also transports glucuronides and sulfate conjugates of steroid hormones and bile salts. It also transports drugs and other hydrophobic compounds in presence of glutathione.
- MRP1 is also involved in multi-drug resistance.

Source: http://nutrigene.4t.com/humanabc.htm

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MRP2 gene

- MRP2 (ABCC2) is expressed in the canalicular (apical) part of the hepatocyte and functions in biliary transport of mainly anionic conjugates with glutathione, with sulfate or with glucuronosyl.
- It is also expressed in other tissues e.g. liver, intestine, kidneys.
- Other substrates of MRP2 include anticancer drugs such as vinblastine (similar specificity as MRP1) and this contributes to drug resistance.

Source: http://nutrigene.4t.com/humanabc.htm

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Conclusion for transporters

- MDR1, MRP1, and MRP2 may be responsible for drug resistance in patients with unsatisfactory seizure control.

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Thank you...

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Genetic polimorphism

- Genetic polymorphism refers to the simultaneous occurrence of the genomes, showing two or more allelic variations at a specific gene locus of chromosomes, in more than 1% of the population.
- These alleles are different from the normal or “wild–type” gene locus by one or multiple mutations, but also gene deletions, duplications or multiplications may also be responsible.

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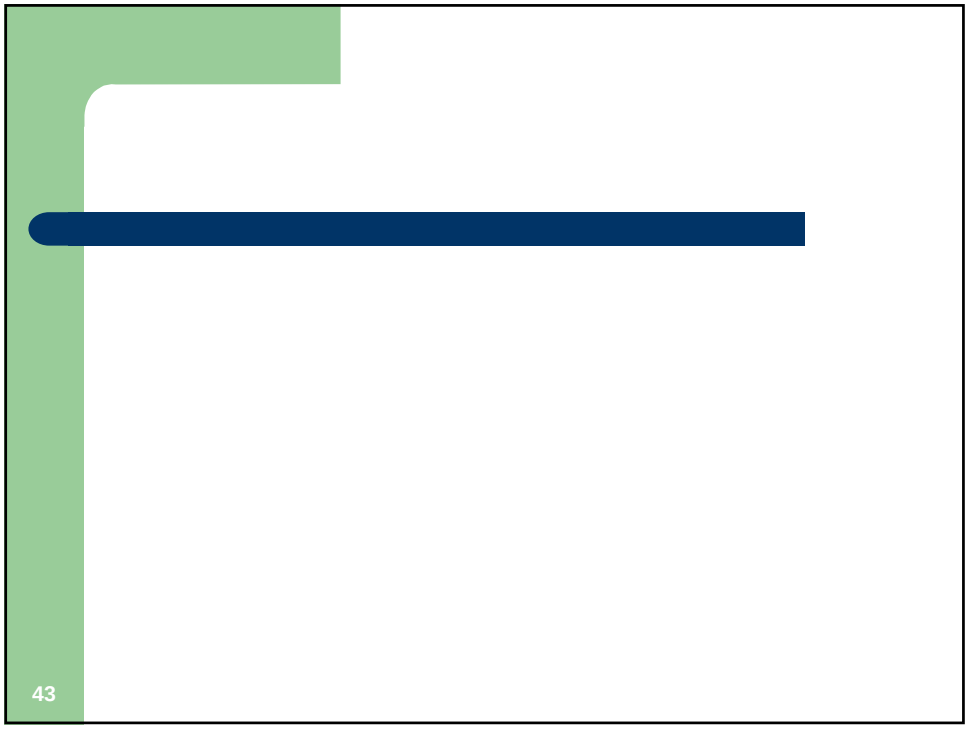
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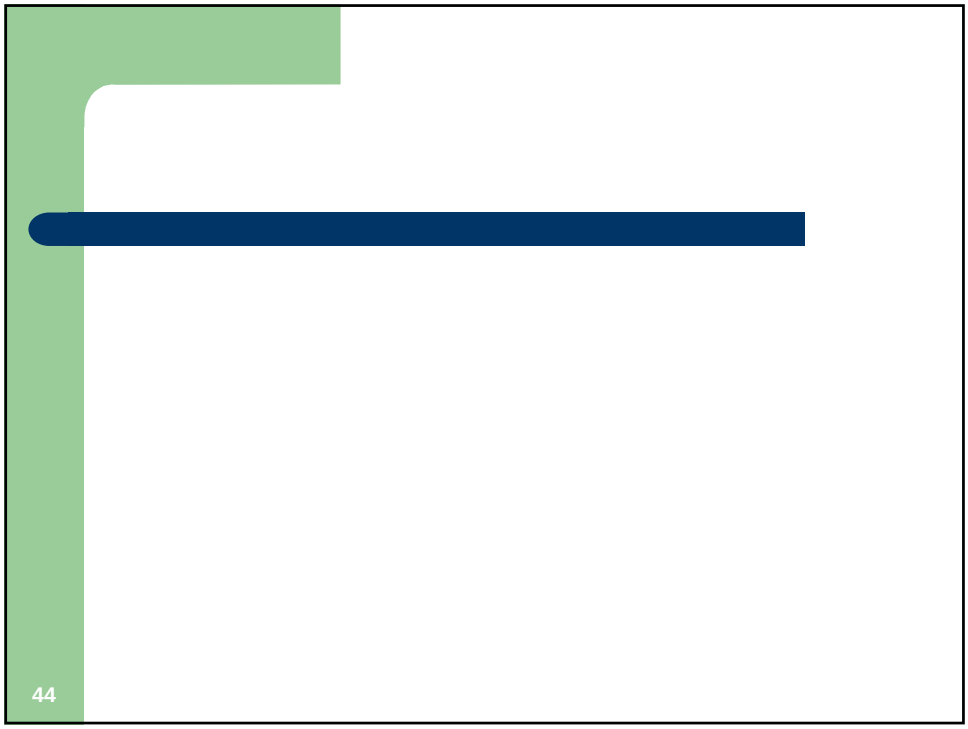
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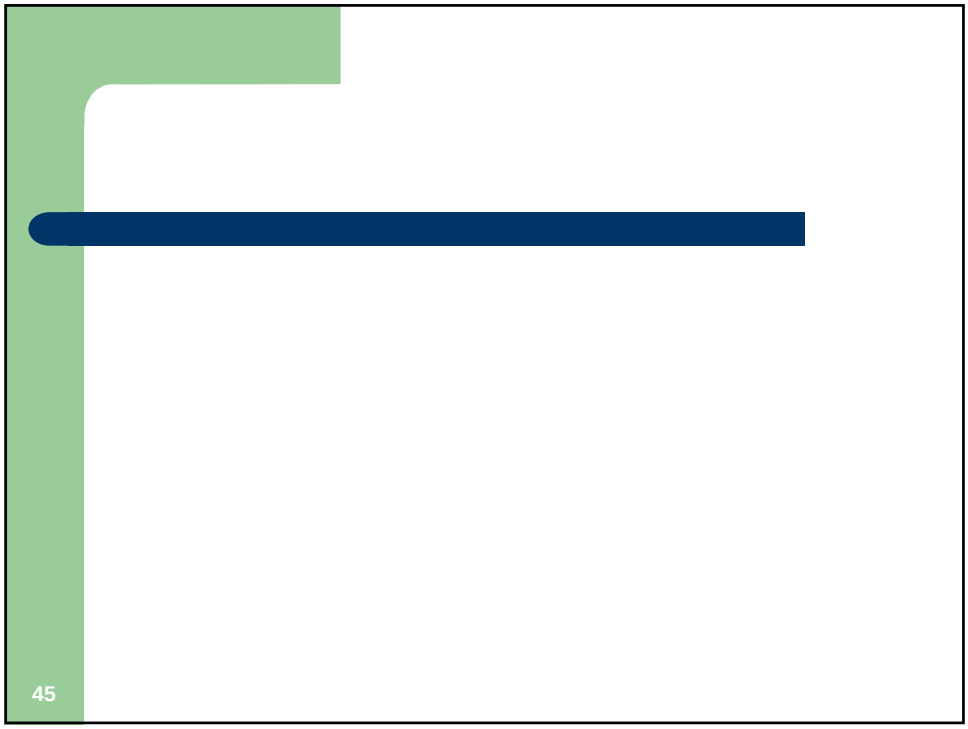
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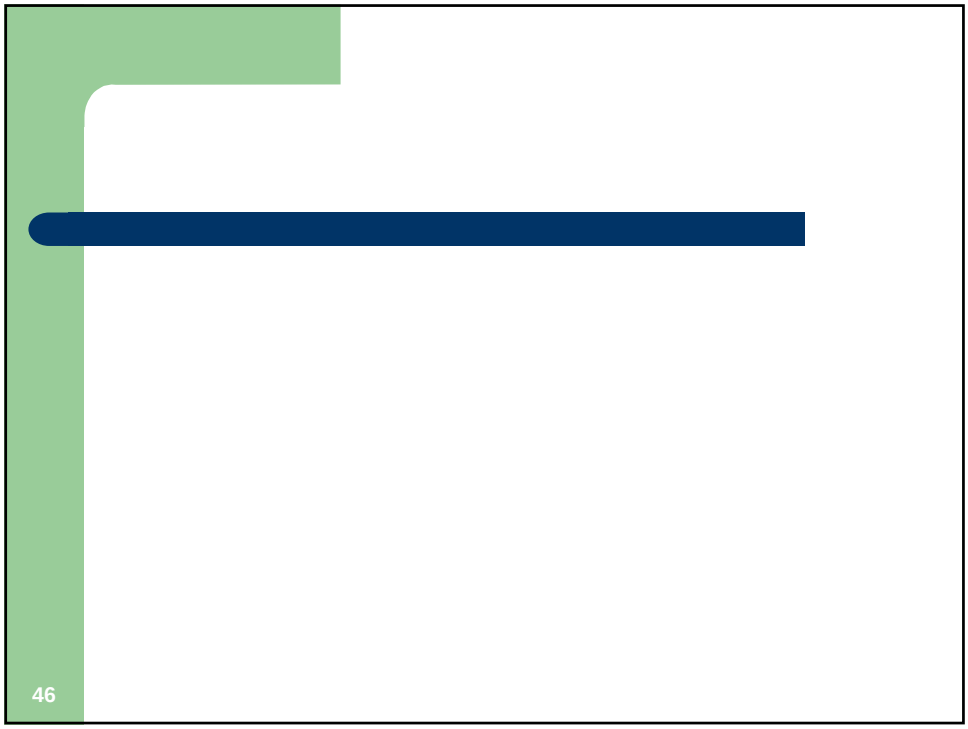
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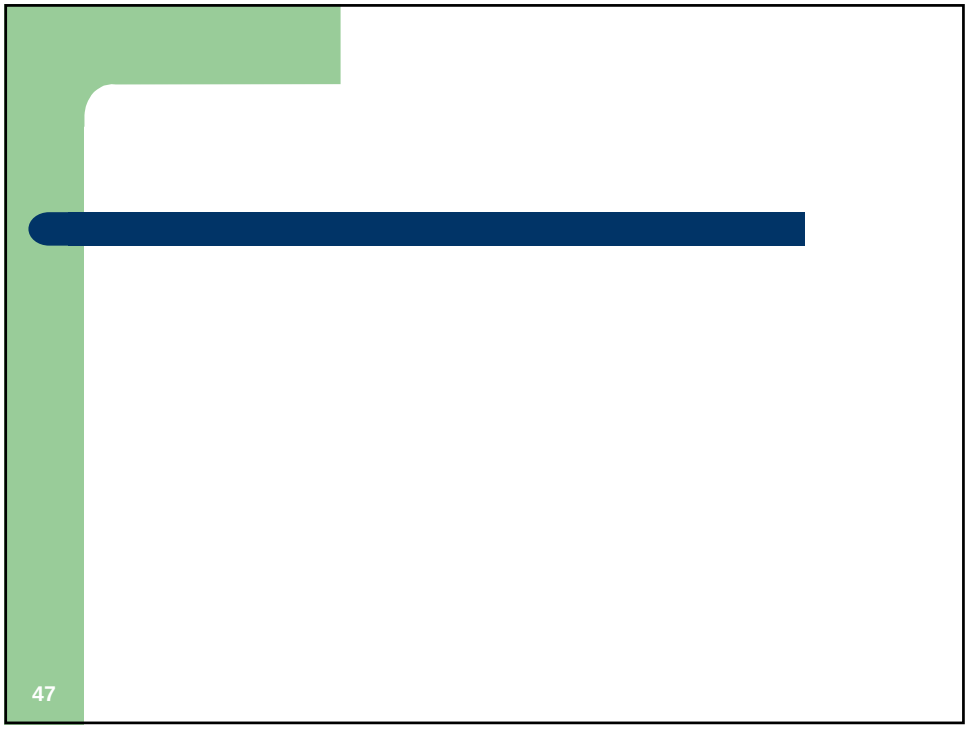
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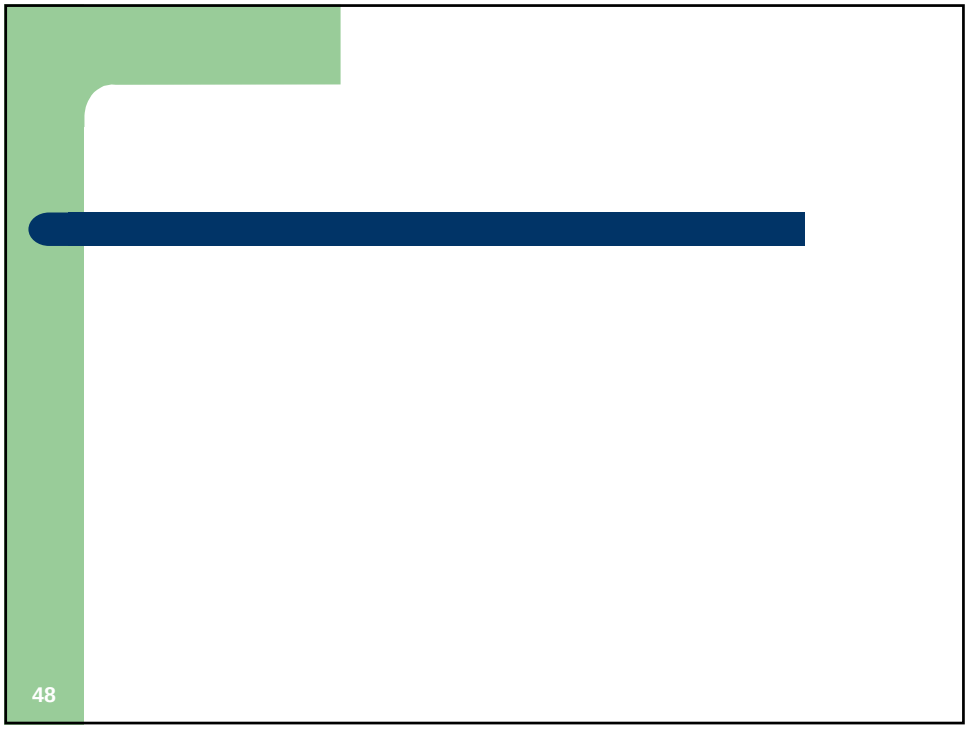
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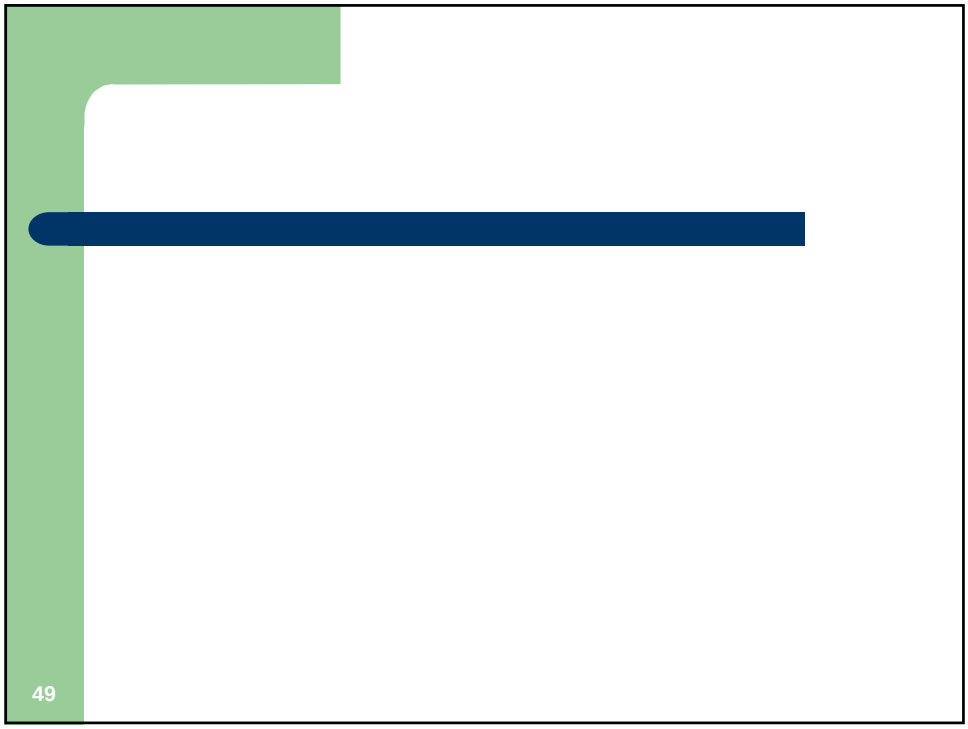
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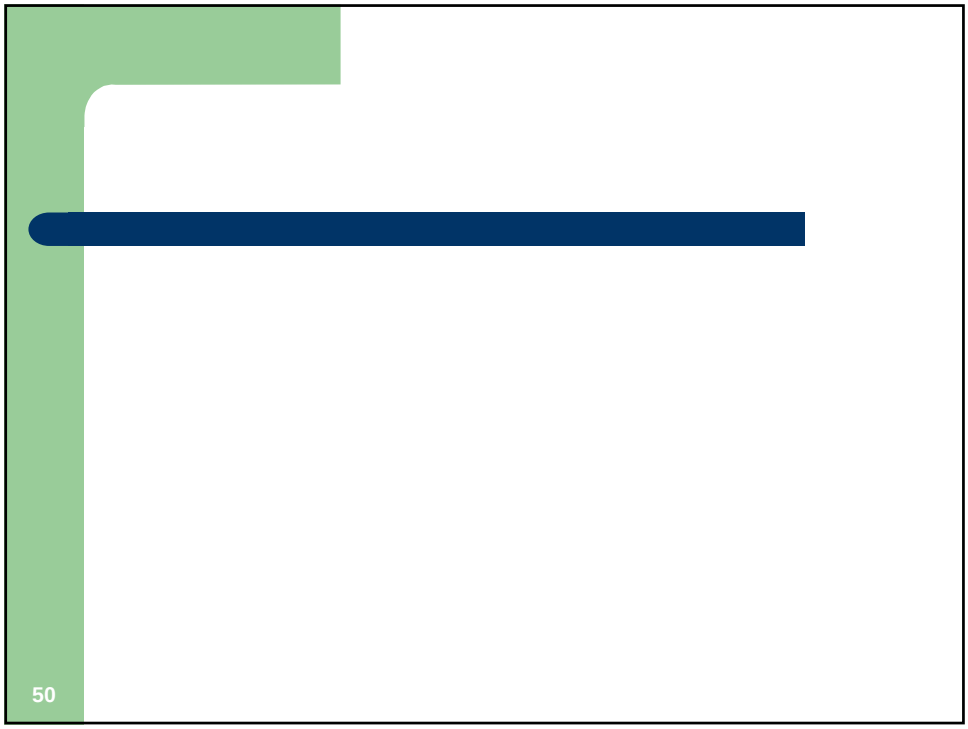
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