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EMBMT
EASTERN MEDITERRANEAN BLOOD AND MARROW TRANSPLANTATION

WCPT Network for HIV/AIDS, Oncology, Hospice and Palliative Care
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INTERNATIONAL ACADEMY FOR CLINICAL HEMATOLOGY
IACH

Impact of Drugs on MSK in Patients undergoing HCT and Organ Transplant

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Every year, nearly two-thirds of the approximately 200,000 patients in need of a bone marrow transplant will not find a marrow donor that matches within their families.

Nathan deal

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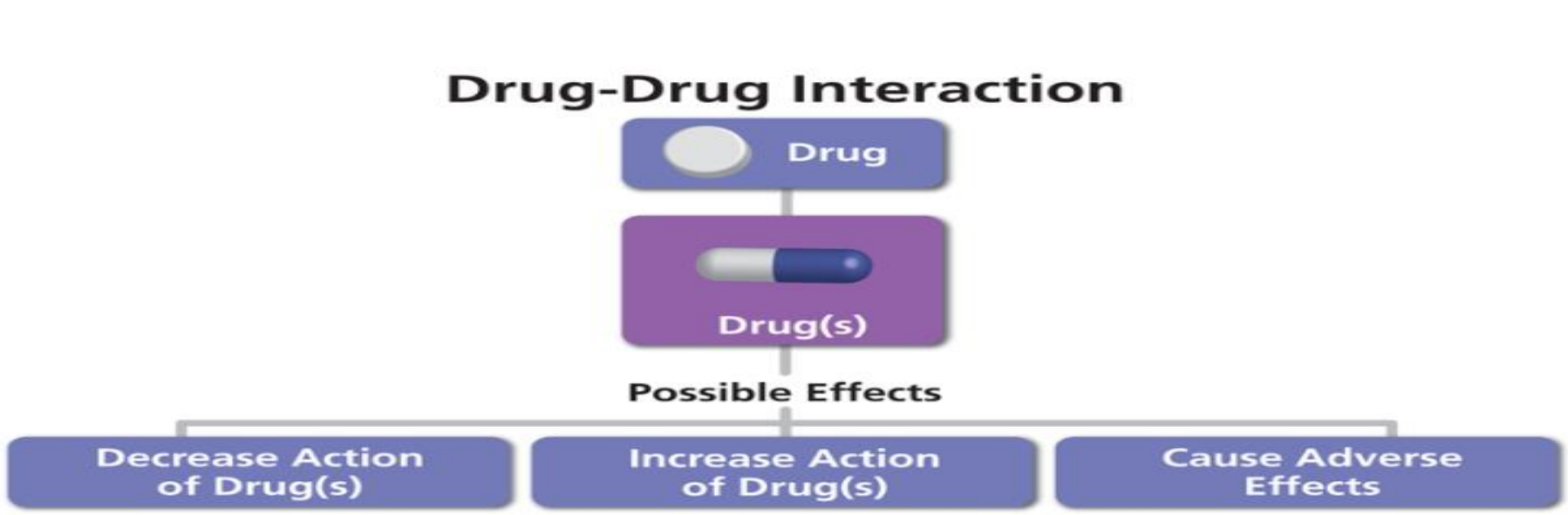
Topics

- What is drug-drug interaction
- What is pharmacokinetics
- What is pharmacodynamics
- What is pharmacogenomics
- Common drug drug interaction in transplant and their impact on MSK
- What is adverse drug reaction
- Case studies

What is drug-drug interaction?

Drug–drug interaction is defined as the change in efficacy or toxicity of one drug by prior or concomitant administration of a second drug.



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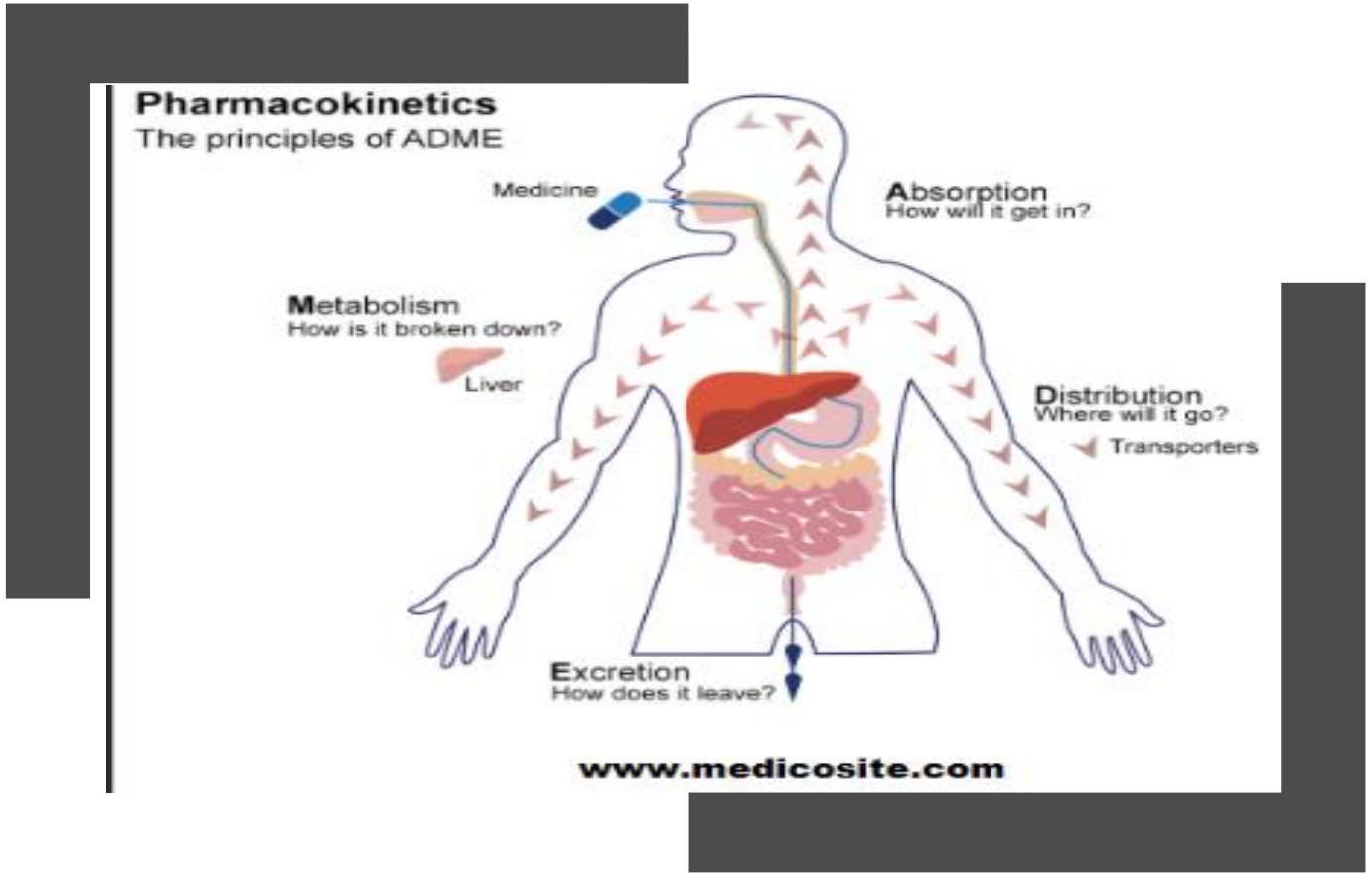
What is pharmacokinetics?



The study of the movement of the drugs in the body, including the process of absorption, distribution, biotransformation and localization in tissues and excretion.

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What is pharmacodynamics?

- Pharmacodynamics is the study of the relationship between the concentration of drug at the site of action and the biochemical and physiological effect.

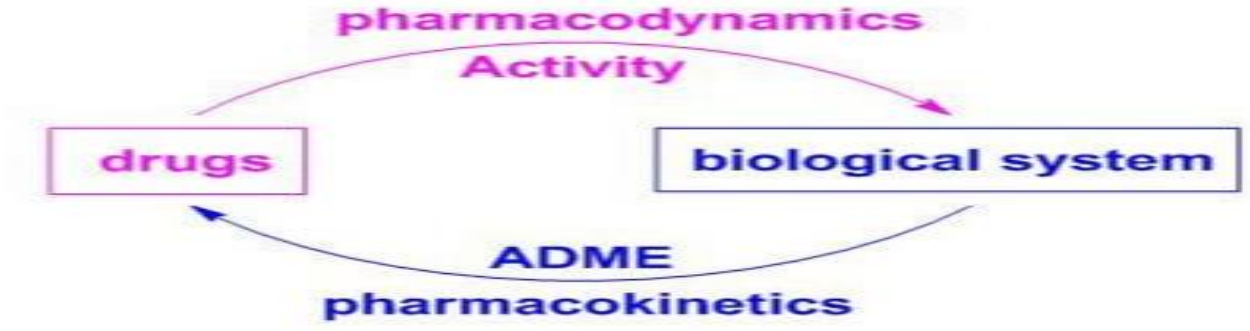
Pharmacokinetics Vs Pharmacodynamics

Pharmacokinetics

Response of the drug to the body

Pharmacodynamics

Response of the body to the drug



What is pharmacogentics\ pharmacogenomics?

Pharmacogenetics is the study of how the actions of and reactions to drugs vary with the patient's genes.

In humans, genes influence race, hair and eye colour, gender, height, weight, aspects of behaviour, and even the likelihood of developing certain diseases. Although some traits are a combination of genetics and environment, researchers are still discovering new ways in which people are affected by their genes

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Pharmacogenomics current concept:

will allow the development of tailored drugs to treat a wide range of health problems, including cardiovascular disease, Alzheimer disease, cancer, HIV/AIDS, and asthma.

What is adverse drug reaction (ADR)

An adverse drug reaction (ADR) is an unwanted or harmful reaction which occurs after administration of a drug or drugs and is suspected or known to be due to the drug(s).

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Cont..

Assessment of undesirable effects is based on the following frequency groupings:

Very common: ≥1/10
Common: ≥1/100 to <1/10
Uncommon: ≥1/1,000 to <1/100
Rare: ≥1/10,000 to <1/1,000
Very rare: <1/10,000
Not known: cannot be estimated from the available data
All of these data

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Prednisolone ADR:

- Total number of serious ADR reports: 2847
- Total number of fatal ADR reports: 490
- The frequency of this ADR with Prednisolone is unknown

Musculoskeletal and connective tissue disorders	**629**	**2**
Bone disorders (excl congenital and fractures)	*112*	*0*
Connective tissue disorders (excl congenital)	*11*	*0*
Fractures	*9*	*0*
Joint disorders	*115*	*0*
Muscle disorders	*190*	*2*
Musculoskeletal and connective tissue deformities (incl intervertebral disc disorders)	*5*	*0*
Musculoskeletal and connective tissue disorders NEC	*158*	*0*
Synovial and bursal disorders	*1*	*0*
Tendon, ligament and cartilage disorders	*28*	*0*

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Prednisone ADR:

- Total number of serious ADR reports: 175
- Total number of fatal ADR reports: 78

- **Musculoskeletal and connective tissue disorders**	**25**	**3**
+ *Bone disorders (excl congenital and fractures)*	*10*	*2*
+ *Fractures*	*1*	*0*
+ *Joint disorders*	*3*	*1*
+ *Muscle disorders*	*5*	*0*
+ *Musculoskeletal and connective tissue disorders NEC*	*6*	*0*

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Cyclosporin ADR:

- Total number of serious ADR reports: 1793
- Total number of fatal ADR reports: 315
- The frequency of this ADR with Cyclosporin:
- Common: myalgia, muscle cramps
- Rare: muscle weakness, myopathy
- Not known: pain of lower extremities

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Cyclosporin ADR:

Musculoskeletal and connective tissue disorders	**234**	**2**
Bone disorders (excl congenital and fractures)	*12*	*0*
Connective tissue disorders (excl congenital)	*9*	*0*
Joint disorders	*49*	*0*
Muscle disorders	*106*	*2*
Musculoskeletal and connective tissue deformities (incl intervertebral disc disorders)	*2*	*0*
Musculoskeletal and connective tissue disorders NEC	*54*	*0*
Synovial and bursal disorders	*1*	*0*
Tendon, ligament and cartilage disorders	*1*	*0*

Tacrolimus ADR:

- Total number of serious ADR reports: 1236
- Total number of fatal ADR reports: 213
- The frequency of this ADR with Tacrolimus:
- Common: arthralgia, muscle cramps, pain in limb, back pain
- Rare: joint disorder
- Not known: mobility disorder

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Tacrolimus ADR:

Musculoskeletal and connective tissue disorders	**67**	**0**
Bone disorders (excl congenital and fractures)	*8*	*0*
Connective tissue disorders (excl congenital)	*1*	*0*
Fractures	*2*	*0*
Joint disorders	*23*	*0*
Muscle disorders	*16*	*0*
Musculoskeletal and connective tissue deformities (incl intervertebral disc disorders)	*1*	*0*
Musculoskeletal and connective tissue disorders NEC	*15*	*0*
Tendon, ligament and cartilage disorders	*1*	*0*

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Sirolimus ADR:

- Total number of serious ADR reports: 245
- Total number of fatal ADR reports: 31
- The frequency of this ADR with Sirolimus:
- Very common: arthralgia
- Common: osteonecrosis

Musculoskeletal and connective tissue disorders	**19**	**0**
Bone disorders (excl congenital and fractures)	*1*	*0*
Joint disorders	*7*	*0*
Muscle disorders	*6*	*0*
Musculoskeletal and connective tissue disorders NEC	*4*	*0*
Synovial and bursal disorders	*1*	*0*

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Statin(Simvastatin) ADR:

- Total number of serious ADR reports: 5568
- Total number of fatal ADR reports: 131
- The frequency of this ADR with Simvastatin:
- Rare: myopathy, rhabdomyolysis with or without renal failure, myalgia, muscle cramps
- Not known: tendinopathy, sometimes complicated by rupture, immune necrotizing myopathy

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Statin(Simvastatin) ADR:

Musculoskeletal and connective tissue disorders	**4173**	**28**
Bone disorders (excl congenital and fractures)	*19*	*0*
Connective tissue disorders (excl congenital)	*28*	*0*
Joint disorders	*560*	*0*
Muscle disorders	*2776*	*28*
Musculoskeletal and connective tissue deformities (incl intervertebral disc disorders)	*10*	*0*
Musculoskeletal and connective tissue disorders NEC	*734*	*0*
Synovial and bursal disorders	*9*	*0*
Tendon, ligament and cartilage disorders	*37*	*0*

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Common drugs in transplant and their impact on MSK

Transplant type	How many drugs	Frequency of drug-drug interaction
Bone marrow transplant	14-18	12
Liver transplant	13-15	6
Lung transplant	14-17	8
Renal transplant	13-17	5

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Lung Transplant – MSK Impact

Drugs	MSK Impact
Amlodipine- Simvastatin	Increase risk of Myopathy-rhabdomyolysis
Cyclosporine- Atorvastatin or Simvastatin	Increase risk of Myopathy-rhabdomyolysis
Itraconazole or Voriconazole - Atorvastatin or Simvastatin	Increase risk of Myopathy-rhabdomyolysis
Isoniazid- Simvastatin	Increase risk of Myopathy-rhabdomyolysis

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Liver Transplant – MSK Impact

Drugs	MSK Impact
Amlodipine- Simvastatin	Increase risk of Myopathy-rhabdomyolysis
Cyclosporine- Atorvastatin or Simvastatin	Increase risk of Myopathy-rhabdomyolysis
Fluconazole-Simvastatin	Increase risk of Myopathy-rhabdomyolysis
Isoniazid- Simvastatin	Increase risk of Myopathy-rhabdomyolysis

Renal Transplant – MSK Impact

Drugs	MSK Impact
Amlodipine+ Simvastatin	Increase risk of Myopathy-rhabdomyolysis
Isoniazid+ Simvastatin	Increase risk of Myopathy-rhabdomyolysis

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HCT Transplant – MSK Impact

Drugs	MSK Impact
Amlodipine- Simvastatin	Increase risk of Myopathy-rhabdomyolysis
Cyclosporine- Atorvastatin or Simvastatin	Increase risk of Myopathy-rhabdomyolysis
Itraconazole or Voriconazole - Atorvastatin or Simvastatin	Increase risk of Myopathy-rhabdomyolysis
Isoniazid- Simvastatin	Increase risk of Myopathy-rhabdomyolysis

Drug-induced myopathy may result from several different mechanisms:

- Direct myotoxicity: alcohol, chemotherapeutic agents, cocaine, glucocorticoids, lipid-lowering drugs, antimalarials, colchicine, and zidovudine.
- Immunologically induced inflammatory: D-penicillamine, statin and tumor necrosis factor inhibitor.
- Indirect muscle damage: drug-induced coma with subsequent ischemic muscle compression, drug-induced hypokalemia (eg, diuretics), drug-induced hyperkinetic states (eg, delirium tremens or seizures secondary to alcohol), dystonic states associated with phenothiazines, hyperthermia related to cocaine use, and the neuroleptic malignant syndrome.

Lipid-lowering drugs: Statins

Statins extensively metabolized by cytochrome P450 3A4 that may cause:

- Myositis
- Elevated creatinine kinase level
- Histology shows muscle necrosis
- No inflammation
- Aching
- Weakness
- Decrease exercise tolerance

It is starts by mild myalgia with or without weakness to chronic myopathy with severe weakness and to massive rhabdomyolysis with acute renal failure.

Lipid-lowering drugs: Statins

Monitoring:

- Baseline CK level as reference.
- Patients treated with statins should be counselled to report the new onset of myalgia or weakness

Management:

-Patients with symptomatic or a symptomatic rhabdomyolysis from statins should discontinue the medication

-CK level >10 times upper limit of normal level that felt it is from statin should discontinue the medication

-Patient should drink large quantities of fluids to facilitate renal excretion of myoglobin.

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YellowCard scheme

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Case:

The calcineurin inhibitors (CIs) cyclosporine A and tacrolimus are essential for graft-versus-host disease prophylaxis but are associated with adverse effects, including neurotoxicity.

We report a case of irreversible CI-induced neuropathic pain following . The patient developed dysesthesia, electric shock-like pain, and severe itching followed by intractable analgesic-resistant pain in the lower extremities.

There were no abnormal radiographic findings, and there was no improvement with a reduction of CI dosage or with administration of a calcium channel blocker. These clinical findings are similar to but inconsistent with CI-induced musculoskeletal pain syndromes previously reported in organ transplantation.

Study:

The aim of this study is to clarify the factors affecting physical function after allogenic HSCT.

retrospectively analysed 88 patients (median age, 44.5 years) who received allogeneic HSCT. Leg extension torque and peak oxygen consumption (VO_2) were evaluated before and after HSCT. Patient factors (age, sex, underlying diseases, hemoglobin, serum albumin, and Karnofsky performance status score before transplant) and transplant factors (conditioning regimen, days to neutrophil engraftment, grades of acute graft-versus-host disease [GVHD], infections, and the interval between pre- and post-evaluation) were collected .
Pre-HSCT leg extension torque, grades of acute GVHD, age, and the interval between pre- and post-evaluation were identified as significant factors associated with reduced post-HSCT leg extension torque. However, none of these factors were significantly associated with reduced post-HSCT peak VO_2, and only its pre-transplant value was identified as a significant factor.

These findings suggest that improvements in muscle strength and cardiopulmonary fitness before HSCT are crucial for maintaining post-treatment physical function, especially in elderly individuals with acute GVHD requiring a long-term stay in a protective environment.

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Study:

Avascular necrosis (AVN) is a debilitating condition reported after chronic steroid use.

Using a retrospective study design, the authors followed 1346 eligible patients for the development of AVN.

The median age at HCT was 34 years (range, 7 months-69 years), and median length of follow-up for those surviving was 8.2 years. Seventy-five patients developed AVN of 160 joints. The cumulative incidence of AVN at 10 years was 2.9% after autologous HCT, 5.4% after allogeneic matched related donor HCT, and 15% after unrelated donor HCT (P<.001 compared with autologous HCT recipients). For allogeneic transplant recipients, male sex (relative risk [RR], 2.1; 95% confidence interval [95% CI], 1.1-4.0); presence of chronic graft-versus-host disease (RR, 2.2); and exposure to CSA, FK506, prednisone, and MMF rendered patients at increased risk, especially in patients with a history of exposure to >or=3 drugs (RR, 9.2; 95% CI, 2.42-35.24).

Thank you !

Questions?

Email: