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**Emerging options of therapy with
Cyclooxygenase 2 inhibitors**

Essay

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for the Master Degree in Internal Medicine***

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**Walid kh. EzzEldeen
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List of Abbreviations

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AA : Arachidonic Acid

A β 42 : β -amyloid peptide 42

ACCF : American College of Cardiology Foundation

ACE : Angiotensin Converting Enzyme

ACEI : Angiotensin Converting Enzyme Inhibitors

ACR : American College of Rheumatology

ACR20: American College of Rheumatology 20% improvement criteria

AD : Alzheimer's disease

ADA : American Diabetes Association

ADC : Adenocarcinoma

ADM : Adenomatous hyperplasia

AF : Atrial fibrillation

AGE : Advanced glycated end-products

AHA : American Heart Association

AIA : Aspirin-intolerant asthma

AKI : Acute Kidney Injury

AMI : Acute Myocardial Infarction

List of Abbreviations

AR : Aldose reductase

ARBs : Angiotensin Receptor Blockers

ARF : Acute Renal Failure

AS : Ankylosing spondylitis

ASA : Aspirin

ATP : Adenosine triphosphate

ATL : Aspirin Triggered Lipoxins

AUC : Area under the Plasma Concentration-time curve

BBB : Blood Brain Barrier

BD : Behcet's Disease

BFGF : Basic Fibroblast Growth Factor

BMD : Bone Mineral Density

BMMSC: Bone Marrow Mesenchymal Stem Cells

CABG : Coronary Artery Bypasses Grafting

Caco-2 : Cancer Colon Cells

CHD : Chronic Heart Disease

CHF : Chronic Heart Failure

CI : Confidence Interval

CL/F : Apparent Plasma Clearance

C max : Peak Plasma Concentration

List of Abbreviations

CNS	: Central Nervous System
COX	: Cyclooxygenase Enzyme
COX-1	: Cyclooxygenase -1 Enzyme
COX-2	: Cyclooxygenase-2 enzyme
CRP	: C reactive protein
CVS	: Cardiovascular Disease
CYP2C9	: Cytochrome P450 2C9
DGR	: Duodeno-Gastric reflux
DIE	: Drug-induced esophageal injury
DILI	: Drug Induced Liver Injury
DPN	: Diabetic Peripheral Neuropathy
EECs	: Endometrial Epithelial Cells
EULAR	: European League Against Rheumatism
F	: Oral bioavailability
FAP	: Familial Adenomatous Polyposis
FDA	: Food and Drug Administration
Fe	: Fraction excreted in unchanged form into urine
Fu	: Fraction of drug unbound in plasma
GCA	: Giant-Cell Arteritis

List of Abbreviations

GI	: Gastro-Intestinal
HIS	: International Headache Society
Ig	: Immunoglobulin
KYNA	: Kynurenic Acid
LOX	: Lipoxygenase
LTA4	: leukotriene A4
LTB4	: leukotriene B4
LTC4	: leukotriene C4
LTD4	: leukotriene D4
LTE4	: leukotriene E4
MMPs	: Matrix Metalloproteinases
MI	: Myocardial Infarction
NADPH	: Nicotinamide adenine dinucleotide phosphate
NF-Kb	: Nuclear Factor Kappa-light-chain-enhancer of activated B cells
NO	: Nitric oxide
O ₂	: Oxygen
OA	: Osteoarthritis
PDGF	: Platelet Derived Growth Factor
PG	: Prostaglandins

List of Abbreviations

PGG2	: Prostaglandins G2
PGH2	: Prostaglandins H2
PGI2	: prostacyclin
PGD2	: Prostaglandins D2
PGF2a	: Prostaglandins F2a
PGE2	: Prostaglandins E2
PLA	: Phospholipase
PKa	: Acid dissociation constant
PKC	: Protein kinase C
POX	: Peroxidase
PPI	: Proton Pump Inhibitors
RA	: Rheumatoid Arthritis
RAGE	: Receptor for advanced glycated end-products
RCT	: Randomized Control Trial
ROS	: Reactive oxygen species
RR	: Relative risk
SLE	: Systemic Lupus Erythematosus
SNC	: Substantia Nigra Pars compacta
SSRI	: Selective Serotonin Reuptake Inhibitors

List of Abbreviations

T _{1/2}	: Elimination Half Life
TIA	: Transient Ischemic Attacks
T _{max}	: Time to maximum plasma concentration
tNSAIDS	: Traditional non-steroidal anti-inflammatory drugs
TNF α	: Tumor necrosis factor α
TNFi	: Tumor necrosis factor-alpha inhibitors
TXA ₂	: Thromboxane A ₂
TXB ₂	: Thromboxane B ₂
ULN	: Upper limit of normal
USPSTF	: United States Preventive Services Task Force
V _{ss}	: Apparent volume of distribution at steady state
5-HPETE	: 5-hydroperoxyeicosatetranoid acid

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Introduction

Cyclooxygenase (COX) enzymes mediate prostaglandin generation. COX-1 is expressed in all cells, producing prostaglandins that maintain cellular homeostasis, and COX-2 is an inducible enzyme that generates inflammatory prostaglandins at sites of inflammation and healing (**Mateos, 2010**).

Nonsteroidal anti-inflammatory drugs (NSAIDs) that non-selectively inhibit COX-1 and COX-2 continue to be an important option for management of pain. However, despite the potential advantages NSAIDs, including their opioid-sparing effect and reduced opioid-related side effects, improved analgesia, and attenuation of the inflammatory pain response; several side effects limit their use. NSAIDs predispose to ulcer formation and upper gastrointestinal bleeding, impaired coagulation, cardiovascular effects and renal dysfunction (**Mateos, 2010**).

A relatively frequent problem with the use of NSAIDs and/or aspirin, and less frequently with paracetamol, is the development of intolerance and hypersensitivity reactions, a situation for which diverse alternatives have been proposed. One of these includes the use of cyclooxygenase 2 specific inhibitors (coxibs) (**Bello and Niembro, 2009**).

Selective cox-2 inhibitors (coxibs) have been shown to possess much improved GI tolerability and reduced GI related