PAIN MANAGEMENT: INDIVIDUALIZED PATIENT CARE VIA COMPOUNDED ADJUNCTIVE THERAPIES

BRETT DINES, RPH MBA

DISCLOSURE OF CONFLICTS

THE PRESENTER HAS EQUITY OWNERSHIP IN APEX COMPOUNDING PHARMACY. THE PRESENTER HAS OBTAINED ACCESS TO THE CITED CLINICAL RESEARCH AND JOURNAL REFERENCES THROUGH HIS FACULTY POSITION AT THE UNIVERSITY OF COLORADO SKAGGS SCHOOL OF PHARMACY AND PHARMACEUTICAL SCIENCES. THE PRESENTERS VIEWS AND OR CLINICAL INTERPRETATION OF THE REFERENCE MATERIAL ARE NOT MEANT TO BE REPRESENTATIVE OF THOSE OF THE UNIVERSITY. THE PRESENTATION HAS BEEN REVIEWED AND APPROVED BY THE SOCIETY OF NURSES IN ADVANCED PRACTICE (SNAP) AND DETERMINED TO BE IN ACCORDANCE WITH ITS POLICY ON OBJECTIVITY IN PROVIDING CONTINUING EDUCATION.

AGENDA

- INTRODUCTION
- WHAT IS COMPOUNDING / REGULATORY CONSIDERATIONS
- CLINICAL RATIONALE
- ROUTE OF DELIVERY
- CLINICAL USE CASES AND REFERENCE FORMULATIONS
- CLINICAL CONSIDERATIONS

EVOLUTION OF COMPOUNDING

- **APOTHECARY:** HOMEOPATHIC AND TAILORED MEDICATIONS
- **FD&C:** DRUG EFFICACY AMENDMENT PL 87-781 (OCTOBER 10, 1962)
- **ADVENT OF MANUFACTURING:** RPH ROLE CHANGES FROM PREPARING TO DISPENSING
- **ECONOMICS CHANGE:** EVOLUTION AND COMMODITIZATION

WHAT IS COMPOUNDING?

PERSONALIZED MEDICINES

- ALLERGIES
- DOSING
- SENSITIVITIES, AVERSION TO ORAL MEDS
- RACE AND ETHNICITY GENETIC EFFECTS: METABOLISM, DISTRIBUTION, ELIMINATION [1]
- SIDE EFFECTS, COMORBIDITIES, DRUG DRUG

REGULATORY CONSIDERATIONS

- NOT A FDA 505(B)1, 505(B)2, OR 505(J)
- NOT A COMMERCIAL COPY
- NOT ON FDA BANNED SUBSTANCE LIST
- 503(A) AND 503(B) EXEMPTED FROM NDA AND LISTED AS A LEGEND DRUG [2]
- DOES REQUIRE A PRESCRIPTION

1) Balmaceda CM, The impact of ethnicity and cardiovascular risk on the pharmacologic management of osteoarthritis: a US perspective. Postgrad Med January 2015, Vol. 127, No. 1 , Pages 51-56

2) US FDA: Compounding Quality Act http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm375804.htm Accessed 03/15/2015

CLINICAL RATIONALE

- DEVELOPED TO ALIGN WITH RECOMMENDATIONS FROM FDA AND SEVERAL PROFESSIONAL MEDICAL ORGANIZATIONS THAT NSAIDS BE USED AT THE LOWEST EFFECTIVE DOSE FOR THE SHORTEST POSSIBLE DURATION CONSISTENT WITH INDIVIDUAL PATIENT TREATMENT GOALS[1]

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[1]U.S. Food and Drug Administration. Public Health Advisory – FDA Announces Important Changes and Additional Warnings for COX-2 Selective and Non-Selective Non-Steroidal Anti-Inflammatory Drugs (NSAIDs).

ROUTE OF ADMINISTRATION AND DISTRIBUTION MULTI COMPARTMENT MODELING

ORAL

- GI: WEAK ACIDS, COX1
- LIVER FIRST PASS
- HIGH PLASMA > LOW TISSUE
- INFLAMMATION IMPACTS INFILTRATION
- T(MAX) ~2.5 BIOLOGICAL HALF LIVES

TRANSDERMAL OR TOPICAL[1,2]

- PENETRATE THE SKIN
  - ~0.55% OF IBU THROUGH STRATUM CORNEUM
- FLUX/ABSORPTION IMPACTED BY BASE
- LOCALIZED EFFECT: HIGH TISSUE > LOW PLASMA
- FASTER TIME TO T(MAX) < 1 BIOLOGICAL HALF LIFE

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1) Kienzler JL. Et al Systemic Bioavailability of topical diclofenac sodium gel 1% versus oral diclofenac sodium in healthy volunteers J Clin Pharmacology 2010;50:50-61

2) Sekiya I et al. Ketoprofen Absorption by Muscle and Tendon after Topical or Oral Administration in Patients Undergoing Anterior Cruciate Ligament Reconstruction AAPS PharmSciTech, Vol. 11, No. 1, March 2010

KINETICS, PEAK PLASMA, AUC(MAX)

DICLOFENAC [1]

DICLOFENAC PHARMACOKINETICS

Table III Summary of Day 7 Plasma Pharmacokinetic Parameters

Treatment	C_{max}, ng/mL	t_{max}, h	AUC_{0-24}, ng h/mL	C_{av}, ng/mL	C_{ss}, ng/mL	PTF, %
A (n = 39)	15.0 ± 7.33	14 (0-24)	233 ± 128	5.92 ± 3.65	9.70 ± 5.32	95.6 ± 40.4
B (n = 39)	53.8 ± 32.0	10 (0-24)	807 ± 478	19.2 ± 12.1	33.6 ± 19.9	106 ± 51.6
C (n = 39)	2270 ± 778	6.5 (1-14)	3890 ± 1710	5.70 ± 3.11	162 ± 71.2	1516 ± 615

All data are mean ± SD, except median (range) for t_{max}. AUC_{0-24}, area under the plasma concentration versus time curve from 0 to 24 hours; C_{av}, average plasma concentration; C_{max}, maximum plasma concentration; C_{ss}, minimum plasma concentration; PTF, peak-trough fluctuation; t_{max}, time to C_{max}. Treatment A = diclofenac sodium topical gel 1% on 1 knee; treatment B = diclofenac sodium topical gel 1% on 2 knees and 2 hands; treatment C = diclofenac sodium 50-mg tablets.

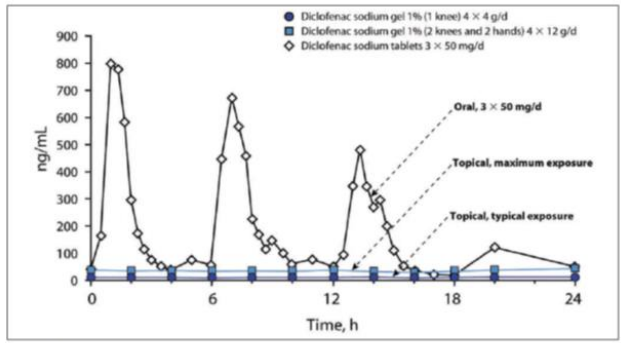
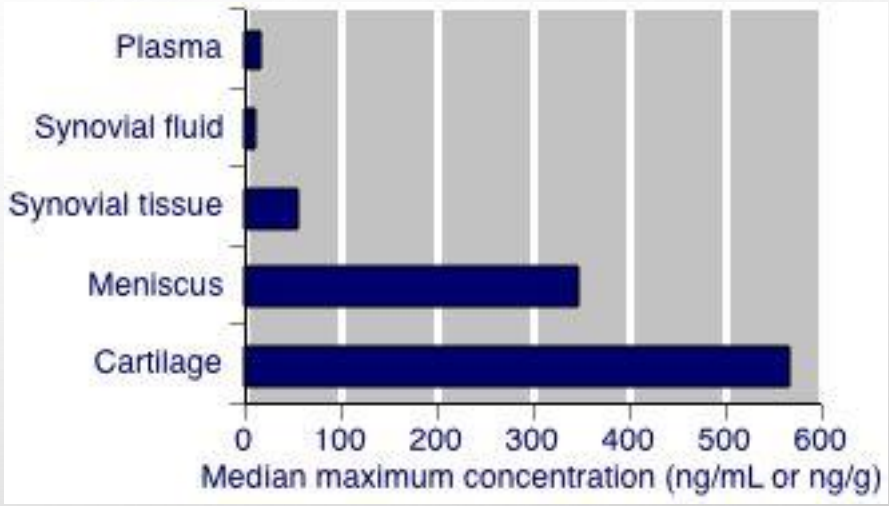


Figure 2. Day 7 plasma absorption of diclofenac from topical versus oral administration. Oral = treatment C (3 × 50 mg/d); topical maximum exposure = treatment B (4 × 12 g/d applied on 2 knees and 2 hands); topical typical exposure = treatment A (4 × 4 g/d applied on 1 knee).

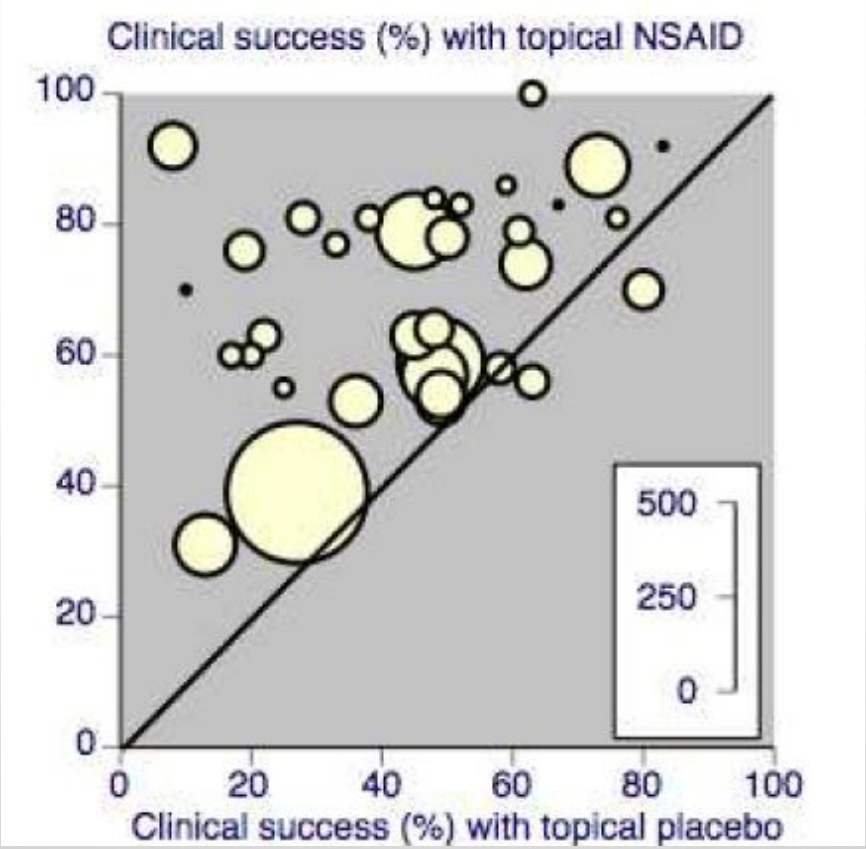
KETOPROFEN [2]



1) Kienzler JL. Et al Systemic Bioavailability of topical diclofenac sodium gel 1% versus oral diclofenac sodium in healthy volunteers J Clin Pharmacology 2010;50:50-61

2) Oxford Press: Bandolier Evidence based thinking about healthcare Topical NSAIDs: penetrating the skin

CLINICAL SUCCESS WITH TOPICAL NSAIDS



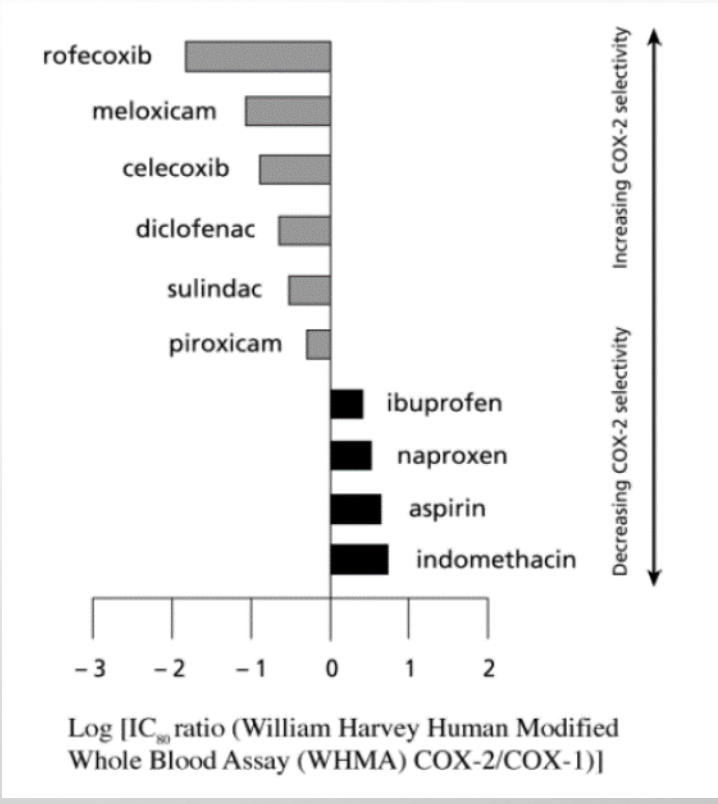
Design: Review of randomized, double blinded controlled trails on efficacy and safety

Size: *47* clinical studies, > 10 patients each.

Clinical Success: Defined as a 50% reduction in pain or equivalent measure … measured on a categorical scale.

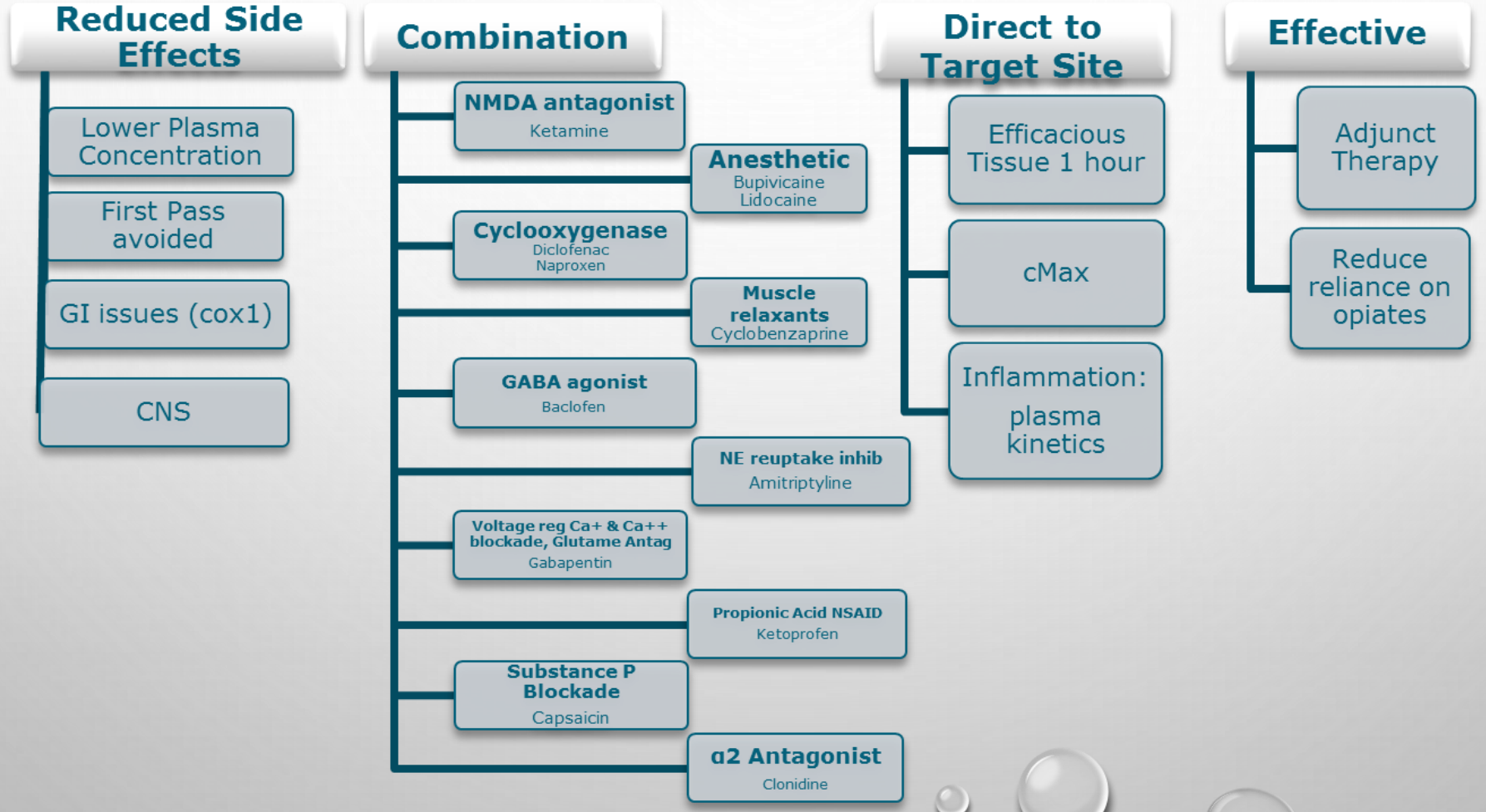
Massey T et al. Topical NSAIDs for acute pain in adults (Review) The Cochrane Collaboration® 2010, Issue 6

CLINICAL RATIONALE

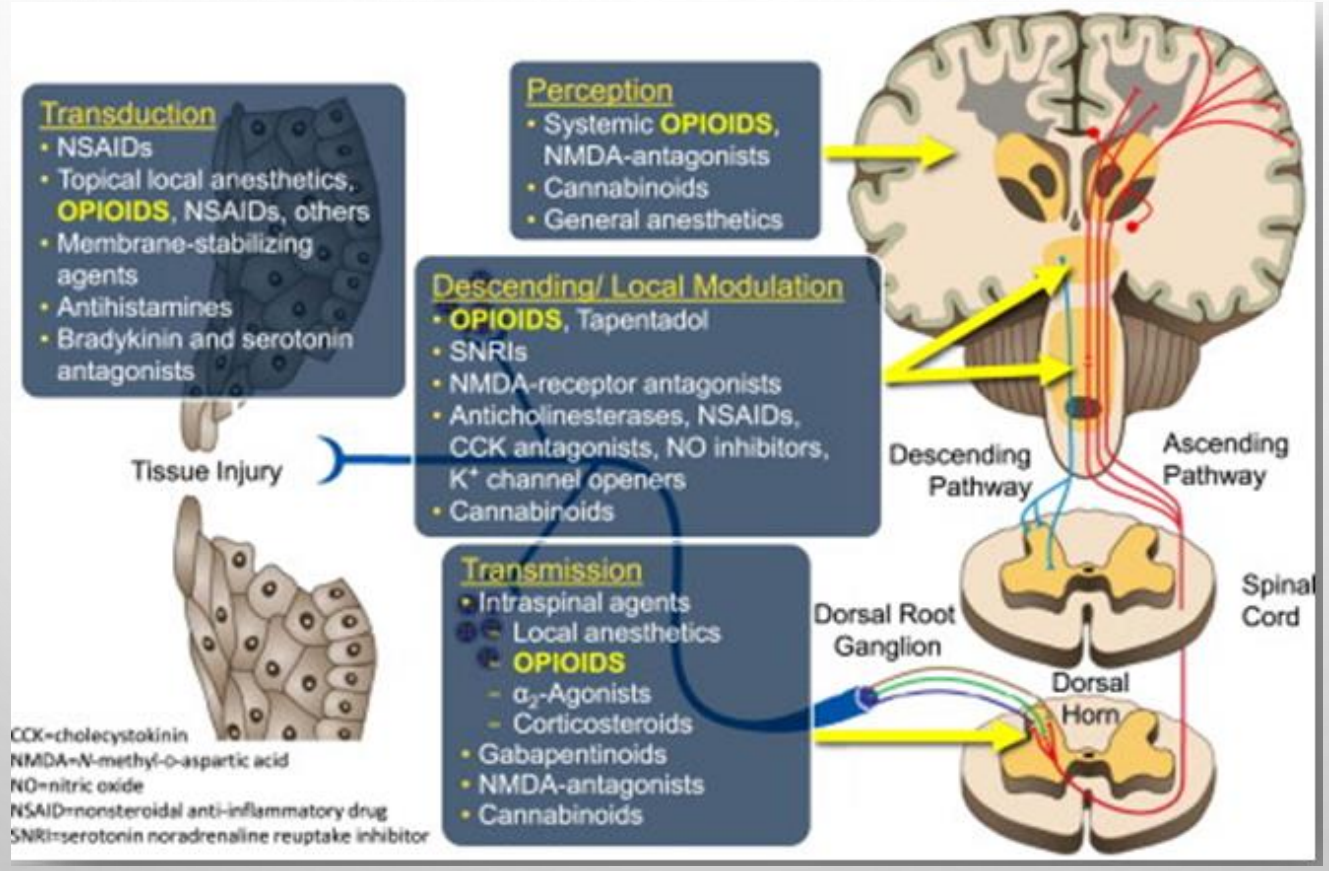


Kerr S, et al. National Prescribing Service Cox-Selective Nsaids: New wonder Drugs ACN 082 034 393

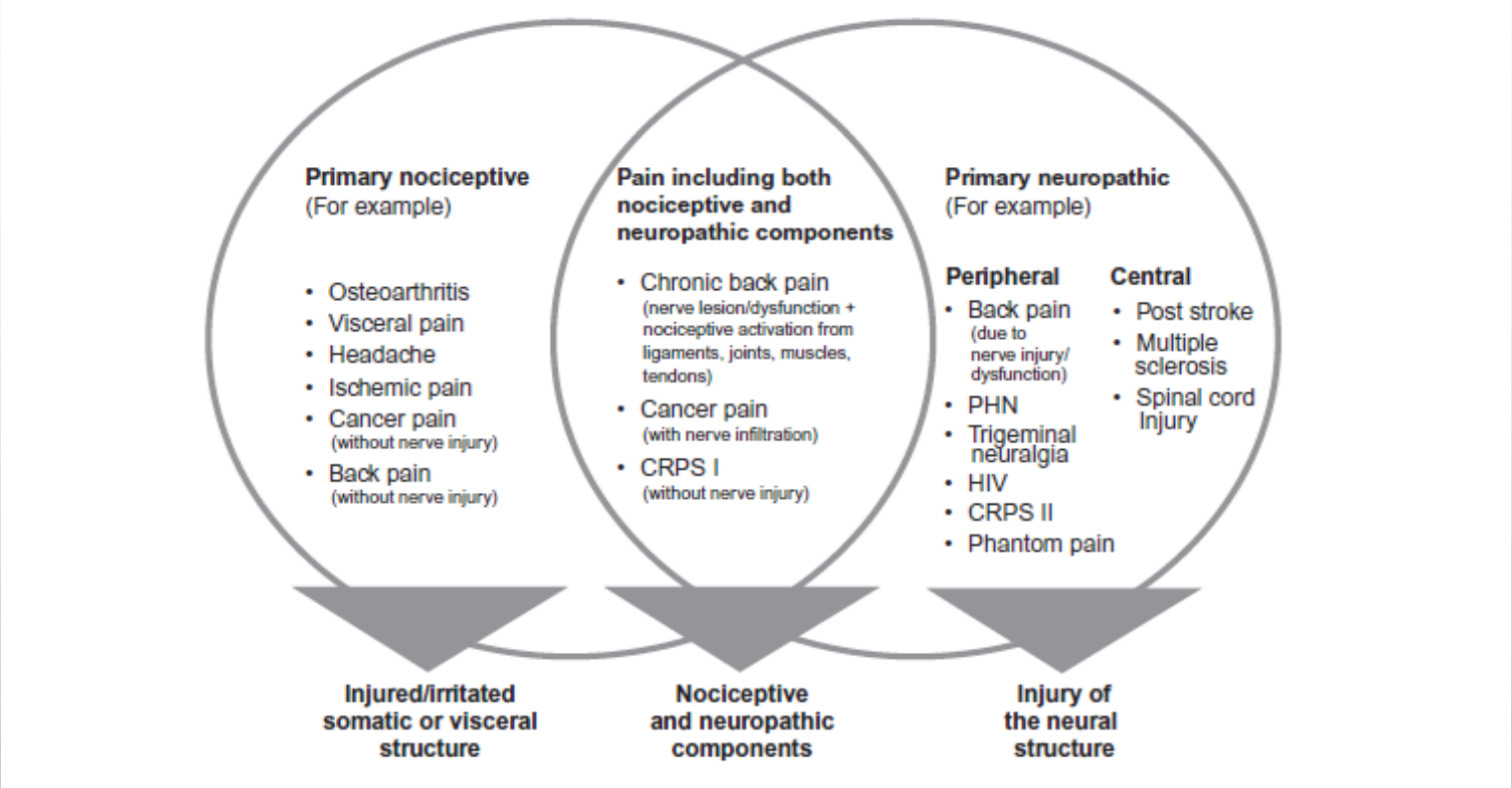
PHARMACOLOGY
FIXED DOSE COMBINATION COMPOUNDS



FIXED DOSE COMBINATION COMPOUNDS



FIXED DOSE COMBINATION COMPOUNDS

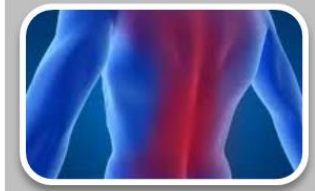


O'Brien J et al. Fixed-dose combinations at the front line of multimodal pain management: perspective of the nurse-prescriber Nursing: Research and Reviews 2013:3 9–22

PHARMACOLOGY AND COMPOUND FORMULA DRIVEN BY ETIOLOGY

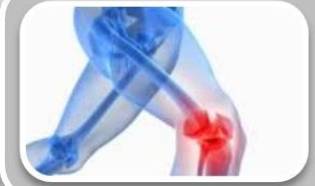
Anti-Inflammatory creams joints & muscles

- Diclofenac 5%, Baclofen 2%, Cyclobenzaprine 2%, Bupivacaine 1%
- Diclofenac 5%, Cyclobenzaprine 2%, Tramadol 10%



Neuropathic pain creams

- Gabapentine 6%, Cyclobenzaprine 2%, Tramadol 10%, Lidocaine 5%, Ketamine 10%
- Gabapentin 6%, Clonidine 0.2%, Imipramine 3%,Lidocaine 5%, Ketamine 10%
- Gabapentin 6%, Carbamazepine 2%, Tramadol 10%, Ketamine 10%

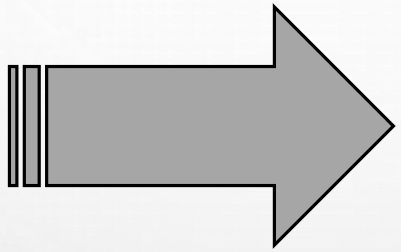


Neuropathic & anti-inflammatory combo creams

- Diclofenac 5%, Gabapentin 6%, Baclofen 2%, Cyclobenzaprine 2%, Bupivacaine 1%, Ketamine 10%

CONSIDERATIONS WITH COMPOUNDED MEDICATIONS CONTRAINDICATIONS AND SIDE EFFECTS

- ANYTHING YOU WOULD MONITOR WITH AN ORALLY ADMINISTERED PRODUCT
- NORMAL SIDE EFFECTS DIMINISHED, BUT NOT LOST



- RENAL INSUFFICIENCY
- DRUG-DRUG INTERACTIONS
- HYPERTENSION: K AND NSAIDS
- NO FLY LIST FOR PILOTS
- COST

QUIZ

QUESTIONS

1) COMPOUNDS MUST COMPLETE THE NEW DRUG APPROVAL PROCESS TO ACHIEVE MARKETING AUTHORIZATION IN THE USA?
2) TOPICAL COMPOUNDS CAN NOT ACHIEVE THE SAME PLASMA CONCENTRATIONS AS ORALLY?
3) TOPICAL DELIVERY CAN RESULT IN A FASTER TIME TO T(MAX) AT THE SITE OF INJURY VS THE ORAL ROUTE OF DELIVERY?
4) FIXED DOSE COMBINATION PRODUCTS USED ADJUNCTIVELY CAN IMPACT OPIATE UTILIZATION?
5) TOPICAL NSAIDS CAN BE USED IN PATIENTS ON PERITONEAL DIALYSIS?

EXAMPLES AND DOSING OF MEDICATIONS USED IN TRANSDERMAL DELIVERY

Drug	Strength	Mechanism
Amitriptyline	1-5%	NE Reuptake inhibitor
Baclofen	2-5%	$GABA_{\beta}$ Agonist
Bretylium	1-5%	Sympathetic Inhibition
Bupivicaine	0.25-10%	Anesthetic
Capsaicin	0.025-0.1%	Substance P Blockade
Carbamazepine	2-5%	NMDA Na^{+} Blocker
Clonidine	0.1-0.3%	Alpha -2 Agonist
Cyclobenzaprine	1-4%	Muscle Relaxant
Dextromethorphan	5-10%	NMDA Receptor Antagonist

EXAMPLES AND DOSING OF MEDICATIONS USED IN TRANSDERMAL DELIVERY

Drug	Strength	Mechanism
Diclofenac	2-10%	Cyclooxygenase Inhibitor
Diphenhydramine	5-10%	Voltage Regulated Na^{+} & Ca^{++} Blockade
Gabapentin	5-10%	Voltage Regulated Na^{+} & Ca^{++} Blockade Glutamate Antagonist
Guaifenesin	5-10%	Muscle Relaxant
Ibuprofen	10-30%	Propionic Acid NSAID
Indomethacin	15-20%	Methylated Indole NSAID
Lidocaine	2-10%	Anesthetic
Lipoic Acid	2-3%	Antioxidant
Loperamide	5-10%	Mu agonist

EXAMPLES AND DOSING OF MEDICATIONS USED IN TRANSDERMAL DELIVERY

Drug	Strength	Mechanism
Naproxen	10-20%	Propionic Acid NSAID
Nifedipine	0.2-16%	Non-NMDA Ca^{+2} Channel Antagonist
Pentoxifylline	5-15%	TNF_{α} Inhibitor, Peripheral Vasodilator
Phenytoin	0.5-2%	NMDA Na^{+} Blocker